

DRUGDEX-EV 2517

MICROMEDEX

DRUGDEX® Evaluations  
Database updated July 2015

## ZIPRASIDONE

[Overview](#)  
[Dosing Information](#)  
[Pharmacokinetics](#)  
[Cautions](#)  
[Clinical Applications](#)  
[References](#)

### 0.0] Overview

#### 1] Class

a) This drug is a member of the following class(es):

Antipsychotic

#### 2] Dosing Information

a) [Ziprasidone](#) Hydrochloride

##### 1] Adult

a) Bipolar I disorder, Acute manic or mixed episodes, monotherapy

1) day 1, 40 mg twice daily with food; day 2, 60 or 80 mg twice daily; then adjust to 40 to 80 mg twice daily [4] [1]

b) Bipolar I disorder, to [lithium](#) or [valproate](#); Adjunct

1) 40 mg to 80 mg twice a day as an adjunct to lithium or valproate [1]

c) [Schizophrenia](#)

1) initial, 20 mg ORALLY twice a day with food; may increase dosage every 2 days up to 80 mg twice a day [4] [1]

2) maintenance, 20 to 80 mg ORALLY twice a day (MAX recommended dose is 80 mg twice a day); to ensure use of the lowest effective dose, observe for improvement for several weeks before upward dosage adjustment [4] [1]

##### 2] Pediatric

a) safety and effectiveness in pediatric patients have not been established [4] [1]

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 [1]

2) Pediatric

a) safety and effectiveness in pediatric patients have not been established [1]

3) Contraindications

a) Ziprasidone Hydrochloride

1) Concomitant administration with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, class IA and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect [20] [4]

2) Heart failure, uncompensated [20] [4]

3) Hypersensitivity to ziprasidone [20] [4]

4) Myocardial infarction, acute and recent [20] [4]

5) QT prolongation, including congenital long QT syndrome, known history of [20] [4]

b) Ziprasidone Mesylate

1) Concomitant administration with arsenic trioxide, chlorpromazine, dofetilide, dolasetron mesylate, droperidol, gatifloxacin, halofantrine, levomethadyl acetate, mefloquine, mesoridazine, moxifloxacin, pentamidine, pimozide, probucol, quinidine, sotalol, sparfloxacin, tacrolimus, thioridazine, class IA and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect [18]

2) Heart failure, uncompensated [18]

3) Hypersensitivity to ziprasidone [18]

4) Myocardial infarction, acute and recent [18]

5) QT prolongation, including congenital long QT syndrome, known history of [18]

**4)) Serious Adverse Effects****a)) Ziprasidone Hydrochloride**

- 1)) Bone marrow depression
- 2)) Diabetes mellitus
- 3)) Drug hypersensitivity syndrome
- 4)) Dysphagia
- 5)) Hyperglycemia
- 6)) Hyperprolactinemia
- 7)) Neuroleptic malignant syndrome
- 8)) Priapism
- 9)) Prolonged QT interval
- 10)) Seizure
- 11)) Syncope
- 12)) Tardive dyskinesia
- 13)) Torsades de pointes

**b)) Ziprasidone Mesylate**

- 1)) Bone marrow depression
- 2)) Diabetes mellitus
- 3)) Drug hypersensitivity syndrome
- 4)) Dysphagia
- 5)) Hyperglycemia
- 6)) Hyperprolactinemia
- 7)) Neuroleptic malignant syndrome
- 8)) Priapism
- 9)) Prolonged QT interval
- 10)) Seizure
- 11)) Syncope
- 12)) Tardive dyskinesia

**13) Torsades de pointes****5) Clinical Applications****a) Ziprasidone Hydrochloride****1) FDA Approved Indications**

- a)** Bipolar I disorder, Acute manic or mixed episodes, monotherapy
- b)** Bipolar I disorder, to [lithium](#) or [valproate](#); Adjunct
- c)** [Schizophrenia](#)

**b) Ziprasidone Mesylate****1) FDA Approved Indications**

- a)** Agitation, acute - [Schizophrenia](#)

**1.0] Dosing Information**[Drug Properties](#)[Storage and Stability](#)[Adult Dosage](#)[Pediatric 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](#)[Ziprasidone Mesylate](#)**C) Physicochemical Properties****1) Molecular Weight**

- a)** 467.42 [205]

**1.2] Storage and Stability****A) Ziprasidone Hydrochloride****1) Preparation**

- a)** Oral route

- 1) Oral ziprasidone hydrochloride capsules and suspension should be taken with food [4] [1].

## B) Ziprasidone Mesylate

### 1) Preparation

#### a) Intramuscular route

##### 1) Preparation

- a) Reconstitute 20 milligram (mg) ziprasidone mesylate vials with 1.2 milliliters (mL) of sterile water for injection. Shake vigorously until all drug is dissolved. Reconstituted solution contains 20 mg/mL, and any unused portion should be discarded [1].

##### 2) Administration

- a) Ziprasidone mesylate injection should only be administered by intramuscular injection (IM) [1].

## C) Ziprasidone Hydrochloride

### 1) Oral route

#### a) Capsule

- 1) Ziprasidone hydrochloride capsules should be stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit) [39].

## D) Ziprasidone Mesylate

### 1) Intramuscular route

#### a) Powder for Solution

- 1) Ziprasidone mesylate for injection, in dry form, should be protected from light and stored at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit). The reconstituted solution is stable for up to 7 days if refrigerated (2 to 8 degrees Celsius (36 to 46 degrees Fahrenheit)) or for up to 24 hours between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit) [39].

## E) Extemporaneous Formulation - Oral route

- 1) To enable oral dosing of ziprasidone in doses lower than 20 mg, ziprasidone mesylate 20 mg/mL for injection was used to create a 2.5 mg/mL oral solution that was chemically and physically stable for 2 weeks under refrigeration when compounded using the following process [206]:

Reconstitute a ziprasidone mesylate vial (equivalent to ziprasidone base 20 mg) with 1.2 mL of distilled water to yield a 20 mg/mL solution.

Further dilute with Ora-Sweet(R) (Paddock Laboratories) to a final concentration of 2.5 mg/mL. Divide into 60 mL brown plastic bottles and store under refrigeration (5 degree C in a dark refrigerator). Stable for 2 weeks.

Dispense with either a calibrated dropper or an oral syringe.

### 1.3] Adult Dosage

#### 1.3.1] Normal Dosage

##### 1.3.1.A] Ziprasidone Hydrochloride

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

###### 1.3.1.A.1.a] Bipolar I disorder, Acute manic or mixed episodes, monotherapy

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 [4] [1].

###### 1.3.1.A.1.b] Bipolar I disorder, to lithium or valproate; Adjunct

1]) For maintenance of bipolar I with adjunctive lithium or valproate, continue the dose of ziprasidone on which the patient was initially stabilized in the range of 40 mg to 80 mg twice a day [1].

###### 1.3.1.A.1.c] 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 [4] [1].

##### 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 of ziprasidone mesylate 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 [1].

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 [3].

### 1.3.2] Dosage in Renal Failure

#### A) Ziprasidone Hydrochloride

1)) No dosage adjustment should be necessary for mild-to-moderate renal impairment. No clinically significant effect on oral ziprasidone pharmacokinetics was found in these patients [4] [1] [16].

#### B) Ziprasidone Mesylate

1)) Ziprasidone mesylate 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 [1].

### 1.3.3] Dosage in Hepatic Insufficiency

#### A) Ziprasidone Hydrochloride

1)) 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 [15].

### 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 [4] [1] [17].

## 1.4] Pediatric Dosage

### 1.4.1] Normal Dosage

#### 1.4.1.A) Ziprasidone Hydrochloride

1)) The safety and effectiveness in pediatric patients have not been established [4] [1].

## 2.0] Pharmacokinetics

### Drug Concentration Levels

### ADME

### 2.2] Drug Concentration Levels

#### A) Ziprasidone Hydrochloride

##### 1)) Time to Peak Concentration

a)) Oral: 6 to 8 hours [56]

1) The ziprasidone C<sub>max</sub> is achieved in approximately 6 to 8 hours after oral administration [56].

**2) Area Under the Curve**

a) Oral, multiple-dose, 20 to 80 mg: dose-proportional [56]

1) Following multiple-dose administration within the recommended clinical dosage range, ziprasidone accumulation is predictable and dose-proportional. Steady-state concentrations are achieved within 1 to 3 days [56] and steady-state pharmacokinetics of ziprasidone did not differ between genders [115].

b) Oral, multiple-dose, [cirrhosis](#), 20 mg: increased 13% and 34% [56]

1) In subjects with clinically significant cirrhosis who received ziprasidone 20 mg twice daily for 5 days (n=13), the AUC (0 to 12 hours) increased 13% and 34% in subjects with Child-Pugh class A and B cirrhosis, respectively compared with matched controls (n=14) [56].

**B) [Ziprasidone](#) Mesylate**

**1) Time to Peak Concentration**

a) IM: 60 minutes [56]

1) Following a single IM injection of ziprasidone, the C<sub>max</sub> occurred in approximately 60 minutes or less [56].

**2.3] ADME**

**2.3.1] Absorption**

**A) [Ziprasidone](#) Hydrochloride**

**1) Bioavailability**

a) Oral: 60% (in fed state) [56]

1) Ziprasidone is considered well absorbed. Following a dose of ziprasidone 20 mg in the fed state, the absolute bioavailability was approximately 60% [56].

**2) Effects of Food**

a) absorption increased up to 2-fold with high-calorie foods [56] [117]



1j) In the presence of food, ziprasidone absorption is increased up to 2-fold [56]. In the fed state, following multiple doses of ziprasidone 10 to 120 mg/day, the AUC was 109.8 to 1027.9 nanograms x hr/mL [118].

b) Ziprasidone exposure was greatest with administration after a high-calorie meal regardless of fat content in a randomized, 6-way crossover study in patients with psychiatric disorders. Patients with various psychiatric disorders (schizophrenia, schizoaffective disorder, bipolar disorder and psychotic disorder not otherwise specified; n=16; age range, 18 to 65 years; 69% male) received ziprasidone 80 mg twice daily for more than 14 days under the following meal conditions: fasting, low calorie (250 kcal)/low fat, low calorie/high fat, medium calorie (500 kcal)/high fat, high calorie (1000 kcal)/low fat, and high calorie/high fat. Ziprasidone exposure was greatest when administered after a high-calorie meal regardless of fat content (tables). Additionally, mean trough concentrations were greater than 70 nanograms/mL following administration with either a medium calorie/high fat, high calorie/low fat, or high calorie/high fat meal, indicating sufficient concentration for clinical response prior to next dose. The trough concentrations under the other fed states fell below 70 nanograms/mL. Based on the US Food and Drug Administration requirements for bioequivalence, ziprasidone exposure was bioequivalent among fasting, low calorie/low fat, and low calorie/high fat conditions. Similarly, ziprasidone exposure was bioequivalent among the medium calorie/high fat, high calorie/low fat, and high calorie/high fat conditions; however, under these 3 meal conditions, ziprasidone exposure was almost twice the exposure compared with the fasting state [117]:

Ziprasidone versus fasting  
condition ratio\*

	Low cal/ low fat	Low cal/ high fat	Med cal/ high fat	High cal/ low fat
AUC	112%	122%	169%	181%
Cmax	119%	134%	179%	183%
Ctrough	100%	106%	177%	168%

\*following administration  
of morning dose

KEY: Med = medium; cal  
= calorie

c) Results of administration of ziprasidone 20 mg after either an 8 hour fast, immediately after a standard meal (50% to 60% calorie content fat), or 2 hours after a standard meal showed a 69% and 67% higher AUC and Cmax, respectively with immediate administration after a standard meal compared with the fasting state in a 3-way crossover study in healthy male volunteers (n=9; age range, 18 to 45 years). Administration 2 hours after a meal also led to greater exposure than under fasting conditions, but not to the same extent as with the high-fat/high-calorie meal [117].

d) Administration of a single dose of ziprasidone 20 mg, 40 mg, and 80 mg, in ascending order, after an 8 hour fast, then immediately after a standard meal (50% to 60% calorie content fat) showed ziprasidone exposure increased in a dose-proportional manner when administered immediately after a high-fat, high-calorie meal compared with the fasting state in a 6-way crossover study in healthy male volunteers (n=8; age range, 19 to 31 years). In the 20 mg, 40 mg, and 80 mg groups, compared with fasting, the AUC increased by 48%, 87%, and 101%, respective; the Cmax increased by 9%, 63%, and 97%, respectively [117].

e) Administration of ziprasidone 40 mg twice daily for 3 days with either a high-fat (60%) or moderate-fat (30%) meal, or after an 8-hour fast revealed the ziprasidone AUC was 104% and 79% greater with a high-fat and a moderate-fat meal, respectively compared with the fasting state in a randomized, 3-way crossover study in health volunteers (n=14; age range 18 to 45 years). Similarly, the C<sub>max</sub> was 84% and 98% greater, respectively compared with the fasting state. However, comparison of AUC following a high-fat meal and a moderate-fat meal indicated bioequivalent ziprasidone exposure regardless of fat content of the meal [117].

**B) Ziprasidone Mesylate**

**1) Bioavailability**

a) IM: 100% [56]

1) The bioavailability of ziprasidone following IM administration is 100% [56]

**2.3.2] Distribution**

**A) Distribution Sites**

**1) Ziprasidone Hydrochloride**

a) Protein Binding

1) Albumin and alpha-1-acid glycoprotein: greater than 99% [56]

a) Protein binding of ziprasidone, primarily to albumin and alpha-1-acid glycoprotein is greater than 99%. In an in vitro study, the protein binding of ziprasidone was not altered by other highly protein bound agents (warfarin, propranolol). Additionally, ziprasidone did not alter the protein binding of warfarin or propranolol in human plasma [56].

**2) Ziprasidone Mesylate**

a) Protein Binding

1) Albumin and alpha-1-acid glycoprotein: greater than 99% [56]

a) Protein binding of ziprasidone, primarily to albumin and alpha-1-acid glycoprotein is greater than 99%. In an in vitro study, the protein binding of ziprasidone was not altered by other highly protein bound agents (warfarin, propranolol). Additionally, ziprasidone did not alter the protein binding of warfarin or propranolol in human plasma [56].

**B) Distribution Kinetics**

**1) Ziprasidone Hydrochloride**

a) Volume of Distribution

1)) 1.5 L/kg [56]

a)) The mean apparent ziprasidone Vd is 1.5 L/kg [56].

2)) Ziprasidone Mesylate

a)) Volume of Distribution

1)) 1.5 L/kg [56]

a)) The mean apparent ziprasidone Vd is 1.5 L/kg [56].

### 2.3.3] Metabolism

#### A)) Metabolism Sites and Kinetics

1)) Ziprasidone Hydrochloride

a)) Liver: extensive [56]

1)) CYP3A4 is the predominant isoenzyme involved in ziprasidone metabolism [114] [115] Ziprasidone is extensively metabolized by the CYP450 enzyme system in the liver after oral administration to 4 major metabolites (benzisothiazole sulfoxide (BITP), BITP-sulphone, ziprasidone sulfoxide, and S-methyl-dihydroziprasidone). The S-methyl-dihydroziprasidone is rendered after reduction via aldehyde oxidase then methylation via thiol methyltransferase. In vitro studies with human liver microsomes and recombinant enzymes showed the CYP3A4 was the major metabolizing enzyme and CYP1A2 to a much lesser extent. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites. Although ziprasidone is extensively metabolized by the CYP450 enzymatic system, it is unlikely that ziprasidone will interfere with metabolism of other agents metabolized by the CYP450 system [56].

2)) Ziprasidone does not cause clinically significant inhibition of CYP2D6 [116] [114].

2)) Ziprasidone Mesylate

a)) Liver: extensive [56]

1)) CYP3A4 is the predominant isoenzyme involved in ziprasidone metabolism [114] [115]. Ziprasidone is extensively metabolized by the CYP450 enzyme system in the liver after oral administration to 4 major metabolites (benzisothiazole sulfoxide (BITP), BITP-sulphone, ziprasidone sulfoxide, and S-methyl-dihydroziprasidone). The S-methyl-dihydroziprasidone is rendered after reduction via aldehyde oxidase then methylation via thiol methyltransferase. In vitro studies with human liver microsomes and recombinant enzymes showed the CYP3A4 was the major metabolizing enzyme

and CYP1A2 to a much lesser extent. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites. Although ziprasidone is extensively metabolized by the CYP450 enzymatic system, it is unlikely that ziprasidone will interfere with metabolism of other agents metabolized by the CYP450 system [56].

2)) Ziprasidone does not cause clinically significant inhibition of CYP2D6 [116] [114].

## **B)) Metabolites**

### **1)) Ziprasidone Hydrochloride**

#### **a)) benisothiazole sulphoxide (BITP): major, active [56]**

1)) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites [56].

#### **b)) benisothiazole sulphone: major, active [56]**

1)) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites [56].

#### **c)) ziprasidone sulphoxide: major, active [56]**

1)) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites [56].

#### **d)) S-methyl-dihydroziprasidone: major, active [56]**

1)) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites [56].

### **2)) Ziprasidone Mesylate**

#### **a)) benisothiazole sulphoxide (BITP): major, active [56]**

1)) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction

by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites [56].

**b) benisothiazole sulphone: major, active [56]**

**1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites [56].**

**c) ziprasidone sulphoxide: major, active [56]**

**1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites [56].**

**d) S-methyl-dihydroziprasidone: major, active [56]**

**1) The 4 major active metabolites of ziprasidone are rendered via oxidation, reduction, and methylation. About two-thirds of ziprasidone metabolism occurs via reduction by aldehyde oxidase, and one-third via oxidation by CYP450 enzymes, based on the amount of in vivo excretory metabolites [56].**

## **2.3.4] Excretion**

### **A) Kidney**

**1) Ziprasidone Hydrochloride**

**a) Renal Excretion (%)**

**1) approximately 20% with less than 1% unchanged [56]**

**a) Approximately 20% of ziprasidone is excreted in the urine with less than 1% excreted as unchanged drug [56].**

**2) Ziprasidone Mesylate**

**a) Renal Excretion (%)**

**1) approximately 20% with less than 1% unchanged [56]**

**a) Approximately 20% of ziprasidone is excreted in the urine with less than 1% excreted as unchanged drug [56].**

### **B) Feces**

**1) Ziprasidone Hydrochloride**

**a)** approximately 66% with less than 4% unchanged [56]

**1)** Approximately 66% of ziprasidone is excreted in the feces with less than 4% excreted as unchanged drug [56].

**2) Ziprasidone Mesylate**

**a)** approximately 66% with less than 4% unchanged [56]

**1)** Approximately 66% of ziprasidone is excreted in the feces with less than 4% excreted as unchanged drug [56].

**C) Total Body Clearance****1) Ziprasidone Hydrochloride**

**a)** 7.5 mL/min/kg [56]

**1)** Following oral administration, the mean apparent total body clearance of ziprasidone is 7.5 mL/min/kg [56].

**2) Ziprasidone Mesylate**

**a)** 7.5 mL/min/kg [56]

**1)** Following oral administration, the mean apparent total body clearance of ziprasidone is 7.5 mL/min/kg [56].

**2.3.5] Elimination Half-life****A) Parent Compound****1) Ziprasidone Hydrochloride**

**a)** 7 hours, oral [56]

**1)** Following oral dosing within the recommended dosing range the half-life was about 7 hours [56].

**2)** In subjects with clinically significant cirrhosis (Child-Pugh class A/B) who received ziprasidone 20 mg twice daily for 5 days (n=13), the half-life was 7.1 hours compared with 4.8 hours in the control group [56].

**3)** Half-life was dose-dependent at steady-state, which was not observed with single doses. With single doses of ziprasidone 5 to 60 mg, the half-life ranged 3 to 4 hours. With multiple dosing of ziprasidone 5 mg or 20 mg twice daily, the half-life ranged from 4 to 5 hours, and with 40 mg and 60 mg twice daily, the half-life ranges were 8.8

hours and 10 hours, respectively [118] [119] [120]. These changes have minimal clinical relevance.

4)) The half-life increased from 4 to 5 hours with 10 to 40 mg/day to 9 to 10 hours with 80 to 120 mg/day 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 [115].

2)) Ziprasidone Mesylate

a)) 2 to 5 hours [56]

1)) Following a single IM dose of ziprasidone, the mean elimination half-life range was 2 to 5 hours. Little accumulation was observed after 3 days of IM dosing [56].

### 2.3.6] Extracorporeal Elimination

A)) Hemodialysis

1)) Ziprasidone Hydrochloride

a)) Dialyzable: No [56]

1)) Ziprasidone is not removed by hemodialysis [56].

2)) Ziprasidone Mesylate

a)) Dialyzable: No [56]

1)) Ziprasidone is not removed by hemodialysis [56].

## 3.0] Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

### 3.0.A] Black Box WARNING

Ziprasidone Hydrochloride

Oral (Capsule; Suspension)

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared with placebo. Although the causes of death in clinical trials were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden

death) or infectious (eg, pneumonia) in nature. Observational studies suggest that antipsychotic drugs may increase mortality. It is unclear from these studies to what extent the mortality findings may be attributed to the antipsychotic drug as opposed to patient characteristics. Ziprasidone hydrochloride is not approved for the treatment of elderly patients with dementia-related psychosis [20] [4].

## Ziprasidone Mesylate

### Intramuscular (Powder for Solution)

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared with placebo. Although the causes of death in clinical trials were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that antipsychotic drugs may increase mortality. It is unclear from these studies to what extent the mortality findings may be attributed to the antipsychotic drug as opposed to patient characteristics. Ziprasidone mesylate is not approved for the treatment of patients with dementia-related psychosis [18].

## 3.1] Contraindications

### A) Ziprasidone Hydrochloride

- 1) Concomitant administration with [arsenic trioxide](#), [chlorpromazine](#), [dofetilide](#), [dolasetron](#) mesylate, [droperidol](#), [gatifloxacin](#), [halofantrine](#), [levomethadyl acetate](#), [mefloquine](#), [mesoridazine](#), [moxifloxacin](#), [pentamidine](#), [pimozide](#), [probucol](#), [quinidine](#), [sotalol](#), [sparfloxacin](#), [tacrolimus](#), [thioridazine](#), class IA and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect [20] [4]
- 2) [Heart failure](#), uncompensated [20] [4]
- 3) Hypersensitivity to [ziprasidone](#) [20] [4]
- 4) [Myocardial infarction](#), acute and recent [20] [4]
- 5) QT prolongation, including congenital [long QT syndrome](#), known history of [20] [4]

### B) Ziprasidone Mesylate

- 1) Concomitant administration with [arsenic trioxide](#), [chlorpromazine](#), [dofetilide](#), [dolasetron](#) mesylate, [droperidol](#), [gatifloxacin](#), [halofantrine](#), [levomethadyl acetate](#), [mefloquine](#), [mesoridazine](#), [moxifloxacin](#), [pentamidine](#), [pimozide](#), [probucol](#), [quinidine](#), [sotalol](#), [sparfloxacin](#), [tacrolimus](#), [thioridazine](#), class IA and III antiarrhythmics, and other drugs that cause QT prolongation; possible additive QT prolongation effect [18]
- 2) [Heart failure](#), uncompensated [18]
- 3) Hypersensitivity to [ziprasidone](#) [18]
- 4) [Myocardial infarction](#), acute and recent [18]
- 5) QT prolongation, including congenital [long QT syndrome](#), known history of [18]



### 3.2] Precautions

#### A) Ziprasidone Hydrochloride

##### 1) Black Box Warning:

2) -- Increased risk of death among elderly patients with dementia-related psychosis reported (unapproved use) [20] [4]

##### 3) Cardiovascular:

4) -- QT prolongation, possibly resulting in torsade de pointes and sudden death, has been reported; risk increased in patients with bradycardia, hypokalemia, hypomagnesemia, or congenital QTc prolongation, and with concomitant use of other drugs that prolong the QTc interval; monitoring recommended; discontinue with persistent QTc measurements of greater than 500 milliseconds [20] [4]

5) -- Orthostatic hypotension may occur; especially during initial dose titration and in patients with known cardiovascular disease (eg, history of myocardial infarction or ischemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, or at risk for hypotension (eg, dehydration, hypovolemia, and antihypertensive therapy) [20]

##### 6) Dermatologic:

7) -- Potentially fatal drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported; immediately discontinue use if DRESS is suspected and manage medically [19]

8) -- Dose-related rash or urticaria has been reported; discontinue if rash occurs with no alternative cause [20]

##### 9) Endocrine Metabolic:

10) -- Hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) has been reported with atypical antipsychotic use; monitoring recommended [20] [4]

11) -- Patients at risk for or diagnosed with diabetes mellitus at increased risk for worsening glucose control or severe hyperglycemia; monitoring recommended; discontinuation may be warranted [20] [4]

12) -- Metabolic changes (ie, dyslipidemia, body weight gain, and hyperglycemia) have been reported with atypical antipsychotic use; monitoring of weight and blood glucose recommended [21]

13) -- Hyperprolactinemia may occur and may progress to galactorrhea, amenorrhea, gynecomastia, impotence, or decreased bone density [20]

14) -- Use cautiously in conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use), as disruption of body temperature regulation has been reported with antipsychotic agents [20] [4]

##### 15) Gastrointestinal:

16) -- Esophageal dysmotility and aspiration have been reported with antipsychotic drug use, which can progress to aspiration pneumonia [20] [4]

##### 17) Hematologic:

18)) -- Fatal [agranulocytosis](#) has been reported [20] [4]

19)) -- [Leukopenia/neutropenia](#) has been reported, with increased risk among patients with a history of drug-induced [leukopenia/neutropenia](#) or low WBC; monitoring recommended; discontinue use if suspected [20] [4]

20)) Neurologic:

21)) -- Life-threatening [neuroleptic malignant syndrome](#) (NMS) has been reported; immediately discontinue therapy if NMS is suspected; recurrence has been reported with rechallenge; if continued treatment is required consider risk versus benefit and monitor closely [20] [4]

22)) -- Potentially irreversible [tardive dyskinesia](#) may occur, with increased risk among elderly, especially elderly women, and patients treated with higher cumulative doses or longer treatment duration; discontinuation may be required [20] [4]

23)) -- Seizures have been reported; use cautiously among patients with a history of seizures, the elderly, or with comorbidities that lower the seizure threshold [20] [4]

24)) Psychiatric:

25)) -- Suicide risk may be increased; closely monitor patients at high risk for suicidality [20] [4]

26)) Reproductive Effects:

27)) -- [Priapism](#) has been reported; severe cases may require surgical intervention [20] [4]

28)) Respiratory:

29)) -- [Aspiration pneumonia](#) may occur in at-risk patients, as [esophageal dysmotility](#) and aspiration have been reported with antipsychotic drug use [20] [4]

30)) Concomitant Use:

31)) -- Avoid concomitant use with QT-interval prolonging drugs [20]

## B)) [Ziprasidone](#) Mesylate

1)) Black Box Warning:

2)) -- Increased risk of death among elderly patients with dementia-related [psychosis](#) reported (unapproved use) [18]

3)) Cardiovascular:

4)) -- QT prolongation, possibly resulting in [torsade de pointes](#) and sudden death, has been reported; risk increased in patients with bradycardia, hypokalemia, hypomagnesemia, or congenital QTc prolongation, and with concomitant use of other drugs that prolong the QTc interval; monitoring recommended; discontinue with persistent QTc measurements of greater than 500 milliseconds [18]

5)) -- Orthostatic hypotension may occur; especially during initial dose titration and in patients with known [cardiovascular disease](#) (eg, history of [myocardial infarction](#) or [ischemic heart disease](#), [heart failure](#), or conduction abnormalities), [cerebrovascular disease](#), or at risk for hypotension (eg, dehydration, [hypovolemia](#), and [antihypertensive therapy](#)) [18]

**6j) Dermatologic:**

**7j)** -- Potentially fatal drug reaction with [eosinophilia](#) and systemic symptoms (DRESS) has been reported; immediately discontinue use if DRESS is suspected and manage medically [19]

**8j)** -- Dose-related rash or [urticaria](#) has been reported; discontinue if rash occurs with no alternative cause [18]

**9j) Endocrine Metabolic:**

**10j)** -- [Hyperglycemia](#) (some cases extreme and associated with [ketoacidosis](#), [hyperosmolar coma](#), or death) has been reported with atypical antipsychotic use; monitoring recommended; discontinuation may be warranted [18]

**11j)** -- Patients at risk for or diagnosed with [diabetes mellitus](#) at increased risk for worsening glucose control or severe [hyperglycemia](#); monitoring recommended [18]

**12j)** -- Metabolic changes (ie, [dyslipidemia](#), body weight gain, and [hyperglycemia](#)) have been reported with atypical antipsychotic use; monitoring of weight and blood glucose recommended [18]

**13j)** -- [Hyperprolactinemia](#) may occur and may progress to [galactorrhea](#), [amenorrhea](#), [gynecomastia](#), impotence, or decreased bone density [18]

**14j)** -- Use cautiously in conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use), as disruption of body temperature regulation has been reported with antipsychotic agents [18]

**15j) Gastrointestinal:**

**16j)** -- [Esophageal dysmotility](#) and aspiration have been reported with antipsychotic drug use, which can progress to [aspiration pneumonia](#) [18]

**17j) Hematologic:**

**18j)** -- Fatal [agranulocytosis](#) has been reported [18]

**19j)** -- [Leukopenia/neutropenia](#) has been reported, with increased risk among patients with a history of drug-induced [leukopenia/neutropenia](#) or low WBC; monitoring recommended; discontinue use if suspected [18]

**20j) Neurologic:**

**21j)** -- Life-threatening [neuroleptic malignant syndrome](#) (NMS) has been reported; immediately discontinue therapy if NMS is suspected; monitor closely if drug is restarted after condition resolves [18]

**22j)** -- Potentially irreversible [tardive dyskinesia](#) may occur, with increased risk among elderly patients, especially elderly women, and patients treated with higher cumulative doses or longer treatment duration; discontinuation may be required [18]

**23j)** -- Seizures have been reported; use cautiously among patients with a history of seizures, the elderly, or with comorbidities that lower the seizure threshold [18]

**24j) Psychiatric:**

**25j)** -- Suicide risk may be increased; closely monitor patients at high risk for suicidality [18]

26)) Reproductive Effects:

27)) -- Priapism has been reported; severe cases may require surgical intervention [18]

28)) Renal:

29)) -- Use IM form cautiously in patients with impaired renal function [18]

30)) Respiratory:

31)) -- Aspiration pneumonia may occur in at-risk patients, as esophageal dysmotility and aspiration have been reported with antipsychotic drug use [18]

32)) Concomitant Use:

33)) -- Avoid concomitant use with QT-interval prolonging drugs [18]

### 3.3] Adverse Reactions

#### 3.3.1] Cardiovascular Effects

##### 3.3.1.A] Ziprasidone Hydrochloride

###### 3.3.1.A.1] Bradyarrhythmia

a)) An 18-year-old woman with bipolar disorder developed symptomatic bradycardia following treatment with aripiprazole and ziprasidone. The patient was initially hospitalized for symptoms of mania and delusions and was not on any pharmacological therapy. Upon admission, her resting heart rate was 62 beats per minute (bpm), blood pressure was 131/77 mmHg, and laboratory results of CBC, metabolic panel, liver and thyroid function tests were normal. Ziprasidone 80 mg/day was initiated to stabilize her psychotic symptoms. Fourteen hours following her second dose, the patient developed sinus bradycardia with a heart rate between 41 and 48 bpm, a blood pressure of 96/47 mmHg, and a QTc interval of 407 milliseconds (msec). She was asymptomatic and the cause at this time was unknown. Ziprasidone was increased to 120 mg the following day. The patient complained of being lightheaded and her heart rate fell between 31 and 35 bpm, with blood pressure of 100/60 mmHg, and a QTc interval of 410 msec. Her bradycardia resolved and she was discharged on a lower dose of ziprasidone (80 mg/day). The patient was readmitted 3 months later for treatment of psychotic symptoms due to medication nonadherence. At this time her resting heart rate was 69 bpm and her blood pressure was 127/72 mmHg. Due to nonadherence of ziprasidone, the patient was switched to aripiprazole 15 mg/day (which was increased to 20 mg/day on day 2) and lithium carbonate 600 mg twice daily for mood stabilization. The patient developed sinus bradycardia, a syncopal episode, a heart rate of 35 bpm, blood pressure of 80/42 mmHg, and a QTc interval of 444 msec. She was administered normal saline and monitored until her heart rate stabilized. Aripiprazole was discontinued following a total of 3 doses, due to the patient's recent issue of bradycardia with ziprasidone. Lithium was continued and upon discharge she had a resting heart rate of 56 bpm and blood pressure of 108/63 mmHg. Documentation of her normal resting heart rate which dropped subsequently on 2 different occasions suggested that the development of bradycardia is associated with the initiation of either ziprasidone or aripiprazole [36].

###### 3.3.1.A.2] Chest pain

a)) Incidence: 3% [4] [1]

b) In short-term trials, the incidence of chest pain was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) [4] [1].

### 3.3.1.A.3] Hypertension

a) Incidence: 1% to 3% [4] [1]

b) Hypertension was reported frequently (at least 1%) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

c) The incidence of hypertension reported in short-term trials of patients with bipolar mania was 3% for ziprasidone hydrochloride-treated subjects (n=279) compared with 2% for placebo-treated patients (n=136) [4] [1].

### 3.3.1.A.4] Orthostatic hypotension

a) Incidence: at least 1% [4] [39]

b) Postural hypotension was reported frequently in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

c) Postural hypotension has been reported with postmarketing oral ziprasidone hydrochloride use and may be dose-dependent [4].

### 3.3.1.A.5] Prolonged QT interval

a) Incidence: 0.06% [1] [4]

b) QT prolongation is dose-related. It is not yet known whether ziprasidone hydrochloride will cause torsade de pointes or increase the rate of sudden death. In clinical trials, oral ziprasidone increased the QTc interval, compared with placebo, by approximately 10 milliseconds (msec) at the highest dose (160 mg). Baseline QTc interval increased 9 to 14 msec more with oral ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine. During clinical trials, clinically significant QTc interval increases (defined as greater than 500 msec) occurred in 0.06% (2 of 2988) of patients on ziprasidone hydrochloride compared with 0.23% (1 of 440) patients on placebo. Ziprasidone was not suspected to have caused the QTc prolongation [4] [1].

1) The risk of QT prolongation and arrhythmia are increased when potassium and magnesium levels are low. Other risk factors include bradycardia, concomitant use of other drugs that prolong QTc interval, and presence of congenital prolongation of the QT interval. Baseline serum potassium and magnesium measurements should be obtained in patients who are at risk for significant electrolyte disturbances before starting ziprasidone. Before starting treatment with ziprasidone, hypokalemia and hypomagnesemia should be corrected. Electrolytes should be periodically monitored during therapy. Avoid ziprasidone in patients with histories of significant cardiovascular illness (QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia). Further evaluation, such as Holter monitor, maybe be necessary in patients who experience symptoms (dizziness, palpitations, or syncope) suggestive of torsade de pointes. If the QTc measurement consistently exceeds 500 milliseconds, then ziprasidone should be discontinued [4] [1].

c) Three case reports describe QTc prolongation following treatment with ziprasidone. The first patient, a 40-year-old man, was previously prescribed haloperidol (2.5 mg/day), quetiapine, and zuclopenthixol decanoate for psychotic disorder not otherwise specified. Haloperidol was discontinued due to lack of effect and ziprasidone 80 mg/day was initiated, which was increased to

160 mg/day 3 weeks later. His psychotic symptoms improved. At 14 months into treatment with ziprasidone, his dose was increased to 240 mg/day to control psychotic exacerbation. Ten weeks following dose increase, an ECG revealed a QTc interval of 0.51 seconds (sec). Ziprasidone was decreased to 160 mg/day with initiation of haloperidol (5 mg/day) and biperiden (2 mg/day) to avoid exacerbation. QT prolongation at the subsequent 2-, 16-, and 20-week follow-up were 0.4 sec, 0.41 sec, and 0.35 sec, respectively. The second patient, a 27-year-old woman with schizophrenia previously taking haloperidol and quetiapine (1200 mg/day) was switched to ziprasidone 120 mg/day due to lack of effect. Within 3 days, her dose was increased to 160 mg/day. On day 25 of treatment, an ECG revealed a QTc interval of 0.44 sec. Her dose of ziprasidone and valproic acid were steadily increased to 240 mg/day and 750 mg/day, respectively. An ECG revealed a QTc interval of 0.51 sec. Her valproic acid dose remained the same, and ziprasidone was decreased to 160 mg/day. Following the ziprasidone dose decrease, ECG testing at the first and second week of dose reduction revealed a QTc intervals of 0.41 sec and 0.38 sec, respectively. The third patient, a 45-year-old woman with schizophrenia, was previously prescribed quetiapine, amisulpride, haloperidol (5 mg/day), risperidone, venlafaxine (150 mg/day), lithium (900 mg/day), and bornaprine hydrochloride (16 mg/day). Haloperidol was switched to ziprasidone (80 mg/day) due to lack of effect. An ECG revealed a QTc interval of 0.4 sec. Two days later, ziprasidone was increased to 160 mg/day and on day 10, an ECG revealed an QTc interval of 0.48 sec. Ziprasidone was discontinued. Ten days later, another ECG revealed a QTc interval of 0.42 sec. All 3 cases demonstrated a temporal relationship between ziprasidone and QTc prolongation [37].

d) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias [22].

### 3.3.1.A.6] Syncope

- a) Incidence: 0.6% [4] [1]
- b) Syncope, which may be more prevalent during initial dose titrations, was reported by 0.6% of patients taking ziprasidone. Patients experiencing syncope may need further evaluation, such as Holter monitoring, to rule out torsade de pointes [4] [1].
- c) The rare occurrence of syncope has been reported during postmarketing use of ziprasidone [4] [1].

### 3.3.1.A.7] Tachycardia

- a) Incidence: 2% [4] [1]
- b) In short-term trials, the incidence of tachycardia was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 1% for placebo-treated subjects (n=273) [4] [1].
- c) Tachycardia occurred frequently (at least 1%) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].
- d) During schizophrenia trials, a mean increase in heart rate of 1.4 beats per minute in the ziprasidone group compared with 0.2 beats per minute in the placebo group. The occurrence of tachycardia has been reported during postmarketing use of ziprasidone [4] [1].

### 3.3.1.A.8] Torsades de pointes

- a) Incidence: rare [4] [1]
- b) Although the development of torsade de pointes, in the presence of other multiple confounding factors, has been observed rarely during postmarketing use of ziprasidone, a causal relationship has not been confirmed. In premarketing studies, the development of torsade de pointes was not observed. Ziprasidone does have the capacity to prolong the QT/QTc interval and prolongation of the QTc interval has been associated with the development of torsade de pointes-type arrhythmias. However,



the association between ziprasidone use and the possible development of *torsade de pointes* has yet to be determined [4] [1].

c) In a case report of a 28-year-old woman, QT prolongation occurred separately during 2 hospital admissions, and asymptomatic nonsustained polymorphic ventricular tachycardia occurred during the second admission while the patient was using ziprasidone concurrently with other potentially arrhythmogenic medications (ie, lithium, ciprofloxacin, fluconazole, fluoxetine, and trazodone). Upon discontinuation of ziprasidone and the other medications, the patient's QT interval shortened. The patient had a medical history of systemic lupus erythematosus, hypothyroidism, and a complicated history of mood disorders with psychotic features, posttraumatic stress disorder, and borderline personality disorder. During the first incidence of QT prolongation (600 milliseconds [msec] at 68 bpm) associated with ziprasidone, the patient was lithium toxic and hypokalemic, either of which has been associated with QT-interval abnormalities and arrhythmias. Discontinuation of ziprasidone and lithium, coupled with emergency dialysis for lithium toxicity, resulted in a decrease in QT interval (440 msec at 77 bpm). Two weeks later, the patient was readmitted with complaints of chest pain and an electrocardiogram revealed prolonged QT interval (540 msec at 58 bpm). The patient experienced a gradual lowering of potassium levels and further prolongation of QT 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 nonsustained 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 [38].

### 3.3.1.B] Ziprasidone Mesylate

#### 3.3.1.B.1] Bradyarrhythmia

- a) Incidence: up to 2% [1]
- b) Bradycardia was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.1.B.2] Hypertension

- a) Incidence: up to 2% [1]
- b) Hypertension was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.1.B.3] Orthostatic hypotension

- a) Incidence: up to 5% [1]
- b) Postural hypotension, reported in up to 5% of patients during short-term fixed-dose trials of IM ziprasidone mesylate, has also been observed during postmarketing use [1].

#### 3.3.1.B.4] Prolonged QT interval

- a) In a study of the QT/QTc prolongation effects of IM ziprasidone mesylate, the mean increase in QTc from baseline to time of maximum plasma concentration following 2 injections of IM ziprasidone mesylate (20 mg then 30 mg, given 4 hours apart) was 4.6 milliseconds (msec) and 12.8 msec following the first and second injections, respectively, compared with 6 msec and 14.7 msec for the first and second injections, respectively, of haloperidol (7.5 mg then 10 mg, given 4 hours apart). No patients experienced a QTc interval exceeding 500 msec in this study [1].

b) QT prolongation is dose-related. It is not yet known whether ziprasidone mesylate will cause *torsade de pointes* or increase the rate of sudden death. In clinical trials, oral ziprasidone hydrochloride increased the QTc interval, compared with placebo, by approximately 10 milliseconds (msec) at the highest dose (160 mg). Baseline QTc interval increased 9 to 14 msec more with oral ziprasidone hydrochloride than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine. During clinical trials, clinically significant QTc interval increases (defined as greater than 500 msec) occurred in 0.06% (2 of 2988) of patients on ziprasidone hydrochloride compared with 0.23% (1 of 440) patients on placebo. Ziprasidone was not suspected to have caused the QTc prolongation [1].

1) The risk of QT prolongation and arrhythmia are increased when potassium and magnesium levels are low. Other risk factors include bradycardia, concomitant use of other drugs that prolong QTc interval, and presence of congenital prolongation of the QT interval. Baseline serum potassium and magnesium measurements should be obtained in patients who are at risk for significant electrolyte disturbances before starting ziprasidone. Before starting treatment with ziprasidone, hypokalemia and hypomagnesemia should be corrected. Electrolytes should be periodically monitored during therapy. Avoid ziprasidone in patients with histories of significant cardiovascular illness (QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia). Further evaluation, such as Holter monitor, maybe be necessary in patients who experience symptoms (dizziness, palpitations, or syncope) suggestive of *torsade de pointes*. If the QTc measurement consistently exceeds 500 milliseconds, then ziprasidone should be discontinued [1].

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias [22].

#### 3.3.1.B.5] Syncope

a) Incidence: 0.6% [1]

b) Syncope, which may be more prevalent during initial dose-titrations, was reported by 0.6% of patients taking ziprasidone. Patients experiencing syncope may need further evaluation, such as Holter monitoring, to rule out *torsade de pointes* [1].

c) The rare occurrence of syncope has been reported during postmarketing use of ziprasidone [1].

#### 3.3.1.B.6] Tachycardia

a) During schizophrenia trials, a mean increase in heart rate of 1.4 beats per minute in the ziprasidone group compared with 0.2 beats per minute in the placebo group. The occurrence of tachycardia has been reported during postmarketing use of ziprasidone [1] [1].

#### 3.3.1.B.7] Torsades de pointes

a) Incidence: rare [1]

b) Although the development of *torsade de pointes*, in the presence of other multiple confounding factors, has been observed rarely during postmarketing use of ziprasidone, a causal relationship has not been confirmed. In premarketing studies, the development of *torsade de pointes* was not observed. Ziprasidone does have the capacity to prolong the QT/QTc interval and prolongation of the QTc interval has been associated with the development of *torsade de pointes*-type arrhythmias. However, the association between ziprasidone use and the possible development of *torsade de pointes* has yet to be determined [1].

#### 3.3.2] Dermatologic Effects



### 3.3.2.A] Ziprasidone Hydrochloride

#### 3.3.2.A.1] Dermal mycosis

- a) Incidence: 2% [1]
- b) In short-term trials, the incidence of fungal dermatitis was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 1% for placebo-treated subjects (n=273) [1].
- c) The incidence of fungal dermatitis reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) [1].
- d) Fungal dermatitis was frequently observed (at least 1 in 100) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

#### 3.3.2.A.2] Rash

- a) Incidence: up to 5% [4] [1]
- b) Development of a dose-dependent rash and/or urticaria was reported in about 5% of patients during premarketing trials with ziprasidone hydrochloride and was one of the more common reasons given for study dropouts [4] [1].
- c) In short-term trials, the incidence of rash was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 3% for placebo-treated subjects (n=273) [4] [1].
- d) Rash was infrequently observed (0.1% to 1%) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

### 3.3.2.B] Ziprasidone Mesylate

#### 3.3.2.B.1] Furunculosis

- a) Incidence: up to 2% [1]
- b) Furunculosis was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.2.B.2] Injection site pain

- a) Incidence: 7% to 9% [1]
- b) Pain at the site of injection was reported in 7% to 9% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.2.B.3] Sweating symptom

- a) Incidence: up to 2% [1]
- b) Sweating was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

### 3.3.3] Endocrine/Metabolic Effects

#### 3.3.3.A] Ziprasidone Hydrochloride

##### 3.3.3.A.1] Abnormal weight gain

- a) Incidence: 0.4% to 10% [4] [1]

- b) Atypical antipsychotic drugs, such as ziprasidone, have been associated with increased cardiovascular or cerebrovascular risk due to metabolic changes, including hyperglycemia, dyslipidemia, and body weight gain [21].
- c) Weight gain was reported in 0.4% and 0.4% of patients on ziprasidone-treated and placebo-treated patients, respectively [4] [1].
- d) 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 hydrochloride 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) [4] [1].

#### 3.3.3.A.2] Diabetes mellitus

- a) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone hydrochloride, increased risk has been clearly associated with other drugs of this class (ie, atypical antipsychotics). In some cases, ketoacidosis, hyperosmolar coma, and death have been reported in patients taking atypical antipsychotics. Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic retesting. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (eg, 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 [4] [1].

#### 3.3.3.A.3] Dyslipidemia

- a) Atypical antipsychotic drugs, such as ziprasidone, have been associated with increased cardiovascular or cerebrovascular risk due to metabolic changes, including hyperglycemia, dyslipidemia, and body weight gain [21].

#### 3.3.3.A.4] Hyperglycemia

- a) Atypical antipsychotic drugs, such as ziprasidone, have been associated with increased cardiovascular or cerebrovascular risk due to metabolic changes, including hyperglycemia, dyslipidemia, and body weight gain [21].
- b) Although there have been few reports of hyperglycemia or diabetes in patients treated with ziprasidone hydrochloride, increased risk has been clearly associated with other drugs of this class (ie, atypical antipsychotics). In some cases, ketoacidosis, hyperosmolar coma, and death have been reported in patients taking atypical antipsychotics. In the patients treated with atypical antipsychotics, ketoacidosis, hyperosmolar coma, or death occurred. Data are presently insufficient to exclude the possibility of increased risk of diabetes due to ziprasidone treatment. Before starting an atypical antipsychotic, patients with risk factors for diabetes should undergo fasting blood glucose testing, with periodic retesting. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (eg, 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 [4] [1].

#### 3.3.3.A.5] Hyperglycemic hyperosmolar state

a) A case report described the occurrence of a hyperosmolar hyperglycemic state (HHS) in a 26-year-old man following treatment with ziprasidone for schizophrenia. Previously, over 3 years of risperidone therapy (5 mg/day), the patient had experienced significant weight gain (increase from 73.6 kg to 121.8 kg) and had developed an impaired glucose tolerance. Consequently, he was switched from risperidone to ziprasidone 80 mg twice daily. Ten weeks after initiation of ziprasidone, he presented with dizziness, vomiting, and an altered level of consciousness; his glucose level was 1224 mg/dL and blood pH was 7.38. Both polyuria and polydipsia were present in the few days prior. A diagnosis of HHS associated with type 2 diabetes mellitus was made. He was started on IV hydration and insulin (10 units/hr gradually tapered for 72 hours) and his condition stabilized. The patient was discharged 4 days later on metformin 500 mg twice daily and subQ short-acting insulin aspart 26 units, 22 units, and 24 units with breakfast, lunch, and dinner, respectively. Ziprasidone was tapered over a 2-week period and replaced with haloperidol. Approximately 6 weeks after discharge, the patient's glucose levels stabilized with metformin and insulin treatment was stopped. This adverse event was rated as probable on the Naranjo adverse event probability scale [42].

### 3.3.3.A.6] Hyperprolactinemia

#### a) Summary

1) Ziprasidone, like other drugs that antagonize dopamine D2 receptors, has the potential to increase prolactin levels; however, the clinical significance is unknown. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients who received prolactin-elevating compounds. Long-term hyperprolactinemia may lead to reduced bone density when associated with hypogonadism [43].

b) A 16-year-old girl developed hyperprolactinemia 2 weeks after starting treatment with ziprasidone 80 mg twice daily. Along with ziprasidone, she was taking divalproex 500 mg twice daily, which she had been receiving for an unknown period of time. Her medical history consisted of ADHD, posttraumatic stress disorder, psychotic and bipolar spectrum symptoms, and oppositional defiant behavior for which she had been treated with divalproex, quetiapine, and fluoxetine. Two weeks following ziprasidone initiation, she developed galactorrhea and her prolactin level was found to be 68.6 nanogram/mL (normal range, 1.4 to 24.2 nanogram/mL). Ziprasidone was discontinued and aripiprazole 2 mg/day was implemented. Known causes of galactorrhea were investigated and excluded. Three weeks later, her galactorrhea had subsided and her prolactin level was within the normal range [44].

c) Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone [26] [27]. The changes are transient and return to baseline within 12 hours of ziprasidone administration [28] [29].

### 3.3.3.A.7] Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

### 3.3.3.B] Ziprasidone Mesylate

#### 3.3.3.B.1] Abnormal weight gain

a) Atypical antipsychotic drugs, such as ziprasidone, have been associated with increased cardiovascular or cerebrovascular risk due to metabolic changes, including hyperglycemia, dyslipidemia, and body weight gain [24].

#### 3.3.3.B.2] Diabetes mellitus

a) Although there have been few reports of [hyperglycemia](#) or [diabetes](#) in patients treated with [ziprasidone](#) mesylate, increased risk has been clearly associated with other drugs of this class (ie, atypical antipsychotics). In some cases, [ketoacidosis](#), [hyperosmolar coma](#), and death have been reported in patients taking atypical antipsychotics. Data are presently insufficient to exclude the possibility of increased risk of [diabetes](#) due to [ziprasidone](#) treatment. Before starting an atypical antipsychotic, patients with risk factors for [diabetes](#) should undergo fasting blood glucose testing, with periodic retesting. All patients receiving an atypical antipsychotic should be monitored for symptoms of [hyperglycemia](#) (eg, 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 [1].

### 3.3.3.B.3] [Dyslipidemia](#)

a) Atypical antipsychotic drugs, such as [ziprasidone](#), have been associated with increased cardiovascular or cerebrovascular risk due to metabolic changes, including [hyperglycemia](#), [dyslipidemia](#), and body weight gain [24].

### 3.3.3.B.4] [Hyperglycemia](#)

a) Atypical antipsychotic drugs, such as [ziprasidone](#), have been associated with increased cardiovascular or cerebrovascular risk due to metabolic changes, including [hyperglycemia](#), [dyslipidemia](#), and body weight gain [24].

b) Although there have been few reports of [hyperglycemia](#) or [diabetes](#) in patients treated with [ziprasidone](#) mesylate, increased risk has been clearly associated with other drugs of this class (ie, atypical antipsychotics). In some cases, [ketoacidosis](#), [hyperosmolar coma](#), and death have been reported in patients taking atypical antipsychotics. In the patients treated with atypical antipsychotics, [ketoacidosis](#), [hyperosmolar coma](#) or death occurred. Data are presently insufficient to exclude the possibility of increased risk of [diabetes](#) due to [ziprasidone](#) treatment. Before starting an atypical antipsychotic, patients with risk factors for [diabetes](#) should undergo fasting blood glucose testing, with periodic retesting. All patients receiving an atypical antipsychotic should be monitored for symptoms of [hyperglycemia](#) (eg, 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 [1].

### 3.3.3.B.5] [Hyperprolactinemia](#)

#### a) Summary

1) [Ziprasidone](#), like other drugs that antagonize [dopamine](#) D2 receptors, has the potential to increase prolactin levels; however, the clinical significance is unknown. [Galactorrhea](#), [amenorrhea](#), [gynecomastia](#), and impotence have been reported in patients who received prolactin-elevating compounds. Long-term [hyperprolactinemia](#) may lead to reduced bone density when associated with [hypogonadism](#) [25].

b) Prolactin level increases are usually small and seen mainly with higher doses of [ziprasidone](#) [26] [27]. The changes are transient and return to baseline within 12 hours of [ziprasidone](#) administration [28] [29].

### 3.3.3.B.6] [Metabolic syndrome](#)

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - [METABOLIC SYNDROME](#)

### 3.3.4] Gastrointestinal Effects

#### 3.3.4.A] Ziprasidone Hydrochloride

##### 3.3.4.A.1] Abdominal pain

- a) Incidence: at least 1% [4] [1]
- b) Abdominal pain was frequently observed in patients (at least 1 in 100) who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

##### 3.3.4.A.2] Constipation

- a) Incidence: 9% [4] [1]
- b) In short-term trials, the incidence of constipation was 9% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 8% for placebo-treated subjects (n=273) [4] [1].

##### 3.3.4.A.3] Diarrhea

- a) Incidence: 5% [4] [1]
- b) The incidence of diarrhea reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) compared with 4% for placebo-treated patients (n=136) [4] [1].
- c) In short-term trials, the incidence of diarrhea was 5% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 4% for placebo-treated subjects (n=273) [4] [1].

##### 3.3.4.A.4] Dysphagia

- a) Incidence: 0.1% to 2% [4] [1]
- b) Esophageal dysmotility and aspiration have been reported with antipsychotic use, and antipsychotics should be used with caution in patients at risk for aspiration pneumonia [4] [1].
- c) The incidence of dysphagia reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 0% for placebo-treated patients (n=136) [4] [1].
- d) Dysphagia was infrequently observed (0.1% to 1%) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

##### 3.3.4.A.5] Edema of the tongue

- a) Incidence: 0.1% to 3% [4] [1]
- b) The incidence of tongue edema reported in short-term trials of patients with bipolar mania was 3% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) [4] [1].
- c) Tongue edema was infrequently observed (0.1% to 1%) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [39].
- d) The rare occurrence of swollen tongue has been reported during postmarketing use of ziprasidone [4] [39].

##### 3.3.4.A.6] Excessive salivation

- a) Incidence: 4% [4] [1]
- b) The incidence of increased salivation reported in short-term trials of patients with bipolar mania was 4% for ziprasidone hydrochloride-treated subjects (n=279) compared with 0% for placebo-treated patients (n=136) [4] [1].
- c) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of increased salivation and the dose of ziprasidone hydrochloride [4] [1].

#### 3.3.4.A.7] Indigestion

- a) Incidence: 8% [4] [1]
- b) In short-term trials, the incidence of dyspepsia was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 7% for placebo-treated subjects (n=273) [4] [1].

#### 3.3.4.A.8] Loss of appetite

- a) Incidence: 2% [4] [1]
- b) In short-term trials, the incidence of anorexia was 2% among ziprasidone hydrochloride-treated schizophrenic subjects (n=702) compared with 1% for placebo-treated subjects (n=273). [4] [1].
- c) Anorexia was frequently observed in patients (at least 1 of 100) who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].
- d) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of anorexia and the dose of ziprasidone hydrochloride [4] [1].

#### 3.3.4.A.9] Nausea

- a) Incidence: 10% [4] [1]
- b) The incidence of nausea reported in short-term trials of patients with bipolar mania was 10% for ziprasidone hydrochloride-treated subjects (n=279) compared with 7% for placebo-treated patients (n=136) [4] [1].
- c) In short-term trials, the incidence of nausea was 10% among ziprasidone hydrochloride-treated schizophrenic subjects (n=702) compared with 7% for placebo-treated subjects (n=273) [4] [1].

#### 3.3.4.A.10] Vomiting

- a) Incidence: 1% to 5% [4] [1]
- b) The incidence of vomiting reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) compared with 2% for placebo-treated patients (n=136) [4] [1].
- c) Vomiting was frequently observed in patients (at least 1 in 100) who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) and was one of the more common reasons given for study dropouts during the bipolar mania trials [4] [1].

#### 3.3.4.A.11] Xerostomia

- a) Incidence: 4% to 5% [4] [1]
- b) The incidence of dry mouth reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) compared with 4% for placebo-treated patients (n=136) [4] [1].

- c) In short-term trials, the incidence of dry mouth was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) [4] [1].
- d) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of dry mouth and the dose of ziprasidone hydrochloride [4] [1].

### 3.3.4.B] Ziprasidone Mesylate

#### 3.3.4.B.1] Abdominal pain

- a) Incidence: up to 2% [1]
- b) Abdominal pain was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.4.B.2] Constipation

- a) Incidence: up to 2% [1]
- b) Constipation was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.4.B.3] Diarrhea

- a) Incidence: up to 3% [1]
- b) Diarrhea was reported in up to 3% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.4.B.4] Dysphagia

- a) Esophageal dysmotility and aspiration have been reported with antipsychotic use, and antipsychotics should be used with caution in patients at risk for aspiration pneumonia [4] [1].

#### 3.3.4.B.5] Indigestion

- a) Incidence: 1% to 3% [1]
- b) Dyspepsia was reported in 1% to 3% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.4.B.6] Loss of appetite

- a) Incidence: up to 2% [1]
- b) Anorexia was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.4.B.7] Nausea

- a) Incidence: 4% to 12% [1]
- b) Nausea was reported in 4%, 8%, and 12% of patients during short-term fixed-dose trials of IM ziprasidone mesylate 2 mg, 10 mg, and 20 mg, respectively [1].

#### 3.3.4.B.8] Rectal hemorrhage

- a) Incidence: up to 2% [1]
- b) Rectal hemorrhage was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].



**3.3.4.B.9] Vomiting**

- a) Incidence: up to 3% [1]
- b) Vomiting was reported in up to 3% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

**3.3.5] Hematologic Effects****3.3.5.A] Ziprasidone Hydrochloride****3.3.5.A.1] Agranulocytosis**

- a) Agranulocytosis, including fatal cases, has been related to antipsychotic drug use in clinical trials [1].

**3.3.5.A.2] Bone marrow depression**

- a) Bone marrow suppression, including leukopenia, neutropenia, and cases of thrombocytopenia, some fatal, have occurred with antipsychotic use in clinical studies and been reported in postmarketing surveillance. Patients with preexisting low WBC count or a history of drug-induced leukopenia or neutropenia should have complete blood counts measured frequently, and ziprasidone hydrochloride therapy should be discontinued if WBC counts decline without the presence of other contributive factors. Additionally, if severe neutropenia occurs (absolute neutrophil count less than 1000 cells/mm(3)), ziprasidone hydrochloride should be discontinued and WBC counts should be monitored until the patient has fully recovered [4] [1].

**3.3.5.A.3] Leukopenia**

- a) Incidence: 0.1% to 1% [1] [4]
- b) Leukopenia was reported infrequently (0.1% to 1%) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [1] [4].

**3.3.5.A.4] Neutropenia**

- a) Neutropenia has been related to antipsychotic drug use in clinical trials [1].

**3.3.5.A.5] Thrombocytopenia**

- a) Incidence: less than 0.1% [4]
- b) Thrombocytopenia was reported rarely (less than 0.1%) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4].

**3.3.5.B] Ziprasidone Mesylate****3.3.5.B.1] Agranulocytosis**

- a) Agranulocytosis, including fatal cases, has been related to antipsychotic drug use in clinical trials [1].

**3.3.5.B.2] Bone marrow depression**



a) **Bone marrow suppression**, including **leukopenia**, **neutropenia**, and cases of **thrombocytopenia**, some fatal, have occurred with antipsychotic use in clinical studies and been reported in postmarketing surveillance. Patients with preexisting low WBC count or a history of drug-induced **leukopenia** or **neutropenia** should have **complete blood counts** measured frequently, and **ziprasidone** hydrochloride therapy should be discontinued if WBC counts decline without the presence of other contributive factors. Additionally, if severe **neutropenia** occurs (absolute neutrophil count less than 1000 cells/mm(3)), **ziprasidone** should be discontinued and WBC counts should be monitored until the patient has fully recovered [1].

#### 3.3.5.B.3] **Leukopenia**

a) **Leukopenia** has been related to antipsychotic drug use in clinical trials [1].

#### 3.3.5.B.4] **Neutropenia**

a) **Neutropenia** has been related to antipsychotic drug use in clinical trials [1].

### 3.3.6] **Hepatic Effects**

#### 3.3.6.A] **Ziprasidone Hydrochloride**

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

a) 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 [30] [31] [27].

b) **Ziprasidone** was discontinued in 2 patients in a clinical trial 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 mg/day. The other patient showed elevations of both serum glutamic-oxaloacetic transaminase (SGOT/AST) and SGPT/**ALT** after 8 days of treatment with **ziprasidone** 40 mg/day. Both patients had elevated **GGT** values at baseline. At follow-up, all values had returned or were returning to normal [29].

#### 3.3.6.B] **Ziprasidone Mesylate**

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

a) 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 [30] [31] [27].

### 3.3.7] **Immunologic Effects**

#### 3.3.7.A] **Ziprasidone Hydrochloride**

##### 3.3.7.A.1] **Drug hypersensitivity syndrome**

a) General Information

1) Drug reaction with **eosinophilia** and systemic symptoms (DRESS) has been reported [48].

2) Signs and symptoms include cutaneous reaction (eg, rash or **exfoliative dermatitis**), fever, **eosinophilia**, **lymphadenopathy** and one or more of the following: **hepatitis**, **nephritis**, **pneumonitis**, **myocarditis**, or **pericarditis** [48].

3) Sometimes fatal [48]

- 4) Sign and symptoms have occurred 11 to 30 days after treatment [19].
- b) Prevention and Management

- 1) Discontinue use if suspected [48].
- c) Postmarketing

- 1) Drug reaction with [eosinophilia](#) and systemic symptoms (DRESS) has been reported with postmarketing use [48].

### 3.3.7.B) [Ziprasidone](#) Mesylate

#### 3.3.7.B.1) [Drug hypersensitivity](#) syndrome

- a) General Information

- 1) Drug reaction with [eosinophilia](#) and systemic symptoms (DRESS) has been reported [33].

- 2) Signs and symptoms include cutaneous reaction (eg, rash or [exfoliative dermatitis](#)), fever, [eosinophilia](#), [lymphadenopathy](#) and one or more of the following: [hepatitis](#), [nephritis](#), [pneumonitis](#), [myocarditis](#), or [pericarditis](#) [33].

- 3) Sometimes fatal [33]

- 4) Sign and symptoms have occurred 11 to 30 days after treatment [19].

- b) Prevention and Management

- 1) Discontinue use if suspected [33].

- c) Postmarketing

- 1) Drug reaction with [eosinophilia](#) and systemic symptoms (DRESS) has been reported with postmarketing use [33].

### 3.3.8) Musculoskeletal Effects

#### 3.3.8.A) [Ziprasidone](#) Hydrochloride

##### 3.3.8.A.1) Myalgia

- a) Incidence: 2% [4] [1]

- b) The incidence of myalgia reported in short-term trials of patients with bipolar mania was 2% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 0% for placebo-treated patients (n=136) [4] [1].

- c) Myalgia was frequently observed in patients who received oral [ziprasidone](#) hydrochloride at multiple doses greater than 4 mg/day during premarketing [schizophrenia](#) clinical trials (n=3834) [4] [1].

##### 3.3.8.A.2) [Rhabdomyolysis](#), following correction of [hyponatremia](#) secondary to [psychogenic polydipsia](#)

- a) [Rhabdomyolysis](#), possibly complicated by [ziprasidone](#) therapy, was observed in 1 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](#) 3 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 [creatinine 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 [creatinine 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](#) [47].

### 3.3.9] Neurologic Effects

#### 3.3.9.A] [Ziprasidone](#) Hydrochloride

##### 3.3.9.A.1] [Akathisia](#)

- a) Incidence: 8% to 10% [4] [1]
- b) The incidence of [akathisia](#) reported in short-term trials of patients with bipolar mania was 10% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 5% for placebo-treated patients (n=136) [4] [1].
- c) In short-term trials, the incidence of [akathisia](#) was 8% among [ziprasidone](#) hydrochloride-treated schizophrenic subjects (n=702) compared with 7% for placebo-treated subjects (n=273) [4] [1].
- d) [Akathisia](#) was one of the more common reasons given for study dropouts during the bipolar mania trials [4] [1].

##### 3.3.9.A.2] [Anxiety](#)

- a) Incidence: 5% [4] [1]
- b) The incidence of anxiety reported in short-term trials of patients with bipolar mania was 5% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 4% for placebo-treated patients (n=136). Anxiety was one of the more common reasons given for study dropouts during the bipolar mania trials [4] [1].
- c) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with [schizophrenia](#) revealed a dependent relationship between the development of anxiety and the dose of [ziprasidone](#) hydrochloride [4] [1].

##### 3.3.9.A.3] [Asthenia](#)

- a) Incidence: 5% to 6% [4] [1]
- b) The incidence of asthenia reported in short-term trials of patients with bipolar mania was 6% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 2% for placebo-treated patients (n=136) [4] [1].
- c) In short-term trials, the incidence of asthenia was 5% among [ziprasidone](#) hydrochloride-treated [schizophrenia](#) subjects (n=702) compared with 3% for placebo-treated subjects (n=273) [4] [1].
- d) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with [schizophrenia](#) revealed a dependent relationship between the development of tremor and the dose of [ziprasidone](#) hydrochloride [4] [1].

##### 3.3.9.A.4] Behavior showing reduced motor activity

- a) Incidence: bipolar mania, less than 10%; [schizophrenia](#), less than 5% [4] [1]

b) Hypokinesia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in [schizophrenia](#) trials. Hypokinesia was frequently observed in patients (at least 1 of 100) who received oral [ziprasidone](#) hydrochloride at multiple doses greater than 4 mg/day during premarketing [schizophrenia](#) clinical trials (n=3834) [4] [1].

#### 3.3.9.A.5] [Disturbance in speech](#)

a) Incidence: 2% [4] [1]

b) The incidence of speech disorder reported in short-term trials of patients with bipolar mania was 2% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 0% for placebo-treated patients (n=136) [4] [1].

#### 3.3.9.A.6] [Dizziness](#)

a) Incidence: bipolar mania, 16%; [schizophrenia](#), 8% [4] [1]

b) The incidence of dizziness and lightheadedness reported in short-term trials of patients with bipolar mania was 16% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 7% for placebo-treated patients (n=136). Dizziness was one of the more common reasons given for study dropouts during the bipolar mania trials [4] [1].

c) In short-term trials, the incidence of dizziness and lightheadedness was 8% among [ziprasidone](#) hydrochloride-treated [schizophrenia](#) subjects (n=702) compared with 6% for placebo-treated subjects (n=273) [4] [1].

d) Dizziness may be more prevalent during initial [ziprasidone](#) hydrochloride dose titrations and is dose-dependent. Patients experiencing continued dizziness may need further evaluation, such as [Holter monitoring](#), to rule out [torsade de pointes](#) [4] [1].

#### 3.3.9.A.7] [Dystonia](#)

a) Incidence: bipolar mania, less than 10%; [schizophrenia](#), less than 5% [4] [1]

b) During the first few days after initiating treatment with an antipsychotic medication, symptoms of [dystonia](#) may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with greater severity) with high potency and at higher doses of first generation antipsychotic medications. Male patients and younger age groups appear to be at greater risk for developing acute [dystonia](#) [4] [1].

c) [Dystonia](#) occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in [schizophrenia](#) trials, and was one of the more common reasons given for study dropouts during the bipolar mania trials. [Dystonia](#) was frequently observed (at least 1%) in patients who received oral [ziprasidone](#) hydrochloride at multiple doses greater than 4 mg/day during premarketing [schizophrenia](#) clinical trials (n=3834) [4] [1].

d) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with [schizophrenia](#) revealed a dependent relationship between the development of [dystonia](#) and the dose of [ziprasidone](#) hydrochloride [4] [1].

#### 3.3.9.A.8] [Extrapyramidal disease](#)

a) Incidence: bipolar mania, 31%; [schizophrenia](#), 14% [4] [1]

b) The incidence of extrapyramidal symptoms (EPS) reported in short-term trials of patients with bipolar mania was 31% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 12% for placebo-treated patients (n=136) [4] [1].

c) In short-term trials, the incidence of extrapyramidal symptoms (EPS) was 14% among ziprasidone hydrochloride-treated schizophrenic subjects (n=702) compared with 8% for placebo-treated subjects (n=273). 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 hydrochloride and placebo groups in these trials [4] [1].

d) In clinical trial adverse effect reports for ziprasidone hydrochloride, the manufacturer defines extrapyramidal symptoms to collectively include extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis, and twitching [4] [1].

### 3.3.9.A.9] Extrapyramidal sign

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

### 3.3.9.A.10] Headache

a) Incidence: 18% [4] [1]

b) The incidence of headache reported in short-term trials of patients with bipolar mania was 18% for ziprasidone hydrochloride-treated subjects (n=279) compared with 17% for placebo-treated patients (n=136) [4] [1].

### 3.3.9.A.11] Hypesthesia

a) Incidence: 1% to 2% [4] [1]

b) The incidence of hypesthesia reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) [4] [1].

c) Hypesthesia was frequently observed (greater than 1%) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

### 3.3.9.A.12] Increased muscle tone

a) Incidence: bipolar mania, less than 10%; schizophrenia, less than 5% [4] [1]

b) Hypertonia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Hypertonia was frequently observed in patients (at least 1 of 100) who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

c) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of hypertonia and the dose of ziprasidone hydrochloride [4] [1].

### 3.3.9.A.13] Insomnia

a) Incidence: rare [1] [1]

b) Insomnia has been reported rarely as part of the postmarketing surveillance of ziprasidone hydrochloride [4] [1].

### 3.3.9.A.14] Neuroleptic malignant syndrome

a) Incidence: rare [23]

b) The use of antipsychotic drugs, such as ziprasidone, has been associated with the development of a potentially fatal syndrome referred to as neuroleptic malignant syndrome (NMS). Signs and symptoms include hyperpyrexia, muscle rigidity, altered mental status, autonomic instability, elevated

creatinine phosphokinase, myoglobinuria, and [acute renal failure](#). If NMS is suspected, discontinue [ziprasidone](#) hydrochloride and other nonessential drugs, provide aggressive symptomatic treatment and monitoring, and treat any serious medical problems. Rechallenge antipsychotic treatment with caution, and carefully monitor the patient for symptoms of NMS. Development of NMS has been reported with reintroduction of antipsychotic therapy in a patient with a history of the syndrome [4] [1].

c) [Neuroleptic malignant syndrome](#) (NMS) has been reported rarely as part of the postmarketing surveillance of [ziprasidone](#) hydrochloride [4] [1].

d) [Neuroleptic malignant syndrome](#) (NMS) developed in a 49-year-old female patient after receiving [ziprasidone](#) (20 to 60 mg 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 IV hydration and electrolyte replacement [23].

#### 3.3.9.A.15] Paresthesia

a) Incidence: at least 1% [4] [1]

b) Paresthesia was frequently reported in oral [ziprasidone](#) hydrochloride-treated patients (at least 1 of 100) at multiple doses greater than 4 mg/day during premarketing [schizophrenia](#) clinical trials (n=3834) [4] [1].

#### 3.3.9.A.16] Seizure

a) Incidence: 0.4% [4] [1]

b) Seizures were reported in 0.4% of ziprasidone-treated patients during clinical trials, although confounding factors may have contributed to the occurrence in many of these cases [4] [1].

#### 3.3.9.A.17] Somnolence

a) Incidence: bipolar mania, 31%; [schizophrenia](#), 14% [4] [1]

b) The incidence of somnolence reported in short-term trials of patients with bipolar mania was 31% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 12% for placebo-treated patients (n=136) [4] [1].

c) In short-term trials, the incidence of somnolence was 14% among [ziprasidone](#) hydrochloride-treated [schizophrenia](#) subjects (n=702) compared with 7% for placebo-treated subjects (n=273). The frequency of somnolence appears to be dose-dependent [4] [1].

d) Somnolence may be more prevalent during initial [ziprasidone](#) hydrochloride dose titrations and is dose-dependent. During short-term clinical trials, 0.3% discontinued therapy due to somnolence [4] [1].

#### 3.3.9.A.18] Spasmodic movement

a) Incidence: bipolar mania, less than 10%; [schizophrenia](#), less than 5% [4] [1]

b) Twitching occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in [schizophrenia](#) trials. Twitching was frequently observed in patients (at least 1 of 100) who received oral [ziprasidone](#) hydrochloride at multiple doses greater than 4 mg/day during premarketing [schizophrenia](#) clinical trials (n=3834) [4] [1].

#### 3.3.9.A.19] Spasmodic torticollis



a) A case report described tardive cervical **dystonia** in a 50-year-old woman following **ziprasidone** use. The patient, who was diagnosed with **atypical depression**, was initiated on **ziprasidone** 80 mg/day. Prior to **ziprasidone** initiation, she had not been prescribed any antidepressant medications. After 4 months of treatment, she presented with involuntary neck movements. **Ziprasidone** was gradually discontinued in 20-mg/day increments over 4 days. However, the cervical **dystonia** persisted and became worse. She was initiated on **clonazepam** 12.5 mg/day which was titrated to 150 mg/day, but there was no improvement. Patient and family history showed no serious diseases. Physical examination revealed neck extension and head tilt caused by patterned, repetitive, and spasmodic contraction of her neck muscles. Brain and cervical MRI and other biochemical tests were all normal. A diagnosis of tardive cervical **dystonia** with torticollis was made after ruling out causes of **secondary dystonia** and family history of **dystonia**. She was treated with **botulinum toxin type A** injections in 4 muscles of her neck and spinal area. The treatment was repeated 4 times at 1-month intervals. The patient experienced a significant improvement in neck pain and head deviation after the fourth injection with no recurrence of tardive symptoms after 5 months of follow-up [40].

### 3.3.9.A.20] Summary

a) **Neuroleptic malignant syndrome**, including fatalities, has been reported with the use of antipsychotic drugs [4] [1]. A case report described NMS in a 49-year-old woman following **ziprasidone** use [23]. During the first few days after initiating treatment with an antipsychotic medication, symptoms of **dystonia** may occur in susceptible individuals. Symptoms of **dystonia** can occur at low doses but most often occur with high potency and at higher doses of first generation antipsychotic medications. Male patients and younger age groups appear to be at greater risk for developing acute **dystonia**. Acute and chronic **tardive dyskinesia** and extrapyramidal syndrome have been reported. Extrapyramidal symptoms include extrapyramidal syndrome, hypertonia, **dystonia**, **dyskinesia**, hypokinesia, tremor, paralysis, and twitching. Somnolence, dizziness, headache, and **akathisia** have also been commonly reported with **ziprasidone** use. If symptoms of NMS develop, **ziprasidone** should be discontinued and the patient should be closely monitored. If extrapyramidal symptoms are observed, consideration should be given to discontinuing the drug [4] [1].

### 3.3.9.A.21] Tardive dyskinesia

a) Incidence: rare [1] [4]

b) The use of antipsychotic drugs, such as **ziprasidone**, is a risk factor for the development of **tardive dyskinesia**, potentially irreversible. The risk of developing the syndrome increases with duration of treatment and total cumulative dose. The incidence of the syndrome appears to be highest among the elderly, particularly women. However, any patient may be at risk to develop the syndrome, even after a comparatively brief treatment period at a low dose. Partial or complete resolution may occur with discontinuation of the antipsychotic drug. The goal should be the smallest dose for the shortest duration with periodic treatment reassessment [4] [1].

c) **Tardive dyskinesia** has been reported rarely as part of the postmarketing surveillance of **ziprasidone** hydrochloride [4] [1].

d) **Tardive dyskinesia** developed in a 70-year-old woman 9 weeks following the initiation of **ziprasidone** therapy (100 mg/day) for the treatment of **major depression** with mood-congruent psychotic features. Symptoms included repetitive, involuntary jaw and toe movements [41].

### 3.3.9.A.22] Tremor

a) Incidence: bipolar mania, less than 10%; **schizophrenia**, less than 5% [4] [1]

b) Tremor occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in **schizophrenia** trials. Tremor was frequently observed in patients (at least 1 of 100) who received oral

ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

c) An analysis of four short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of tremor and the dose of ziprasidone hydrochloride [4] [1].

### **3.3.9.B] Ziprasidone Mesylate**

#### **3.3.9.B.1] Akathisia**

a) Incidence: up to 2% [1]

b) Akathisia was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### **3.3.9.B.2] Anxiety**

a) Incidence: up to 2% [4]

b) Anxiety was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [4].

#### **3.3.9.B.3] Asthenia**

a) Incidence: up to 2% [1]

b) Asthenia was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### **3.3.9.B.4] Disturbance in speech**

a) Incidence: up to 2% [1]

b) Speech disorder was reported in up to 2% of patients during short-term fixed-dose IM trials of ziprasidone mesylate [1].

#### **3.3.9.B.5] Dizziness**

a) Incidence: 3% to 10% [1]

b) Dizziness was reported in 3% to 10% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### **3.3.9.B.6] Dystonia**

a) During the first few days of treatment with an antipsychotic medication, symptoms of dystonia may occur in susceptible individuals. Symptoms may include spasm of neck muscles, which may progress to tightening of the throat, swallowing difficulty, breathing difficulty, or protrusion of the tongue. These symptoms can occur at low doses but most often occur (and occur with greater severity) with high potency and at higher doses of first generation antipsychotic medications. Male patients and younger age groups appear to be at greater risk for developing acute dystonia [1].

#### **3.3.9.B.7] Extrapyramidal disease**

a) Incidence: up to 2% [1]

b) Extrapyramidal syndrome was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].



**3.3.9.B.8] Extrapyramidal sign**

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

**3.3.9.B.9] Headache**

a) Incidence: 3% to 13% [1]

b) Headache was reported in 3% to 13% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

**3.3.9.B.10] Insomnia**

a) Incidence: up to 3% [1]

b) Insomnia, reported in up to 3% of patients during short-term fixed-dose trials of IM ziprasidone mesylate, has also been observed during postmarketing use [1].

**3.3.9.B.11] Neuroleptic malignant syndrome**

a) Incidence: rare [23]

b) The use of antipsychotic drugs, such as ziprasidone, has been associated with the development of a potentially fatal syndrome referred to as neuroleptic malignant syndrome (NMS). Signs and symptoms include hyperpyrexia, muscle rigidity, altered mental status, autonomic instability, elevated creatinine phosphokinase, myoglobinuria, and acute renal failure. If NMS is suspected, discontinue ziprasidone and other nonessential drugs, provide aggressive symptomatic treatment and monitoring, and treat any serious medical problems. Rechallenge antipsychotic treatment with caution, and carefully monitor the patient for symptoms of NMS. Development of NMS has been reported with reintroduction of antipsychotic therapy in a patient with a history of the syndrome [4] [1].

c) Neuroleptic malignant syndrome (NMS) has been reported rarely as part of the postmarketing surveillance of oral and IM ziprasidone [4].

d) Neuroleptic malignant syndrome (NMS) developed in a 49-year-old female patient after receiving ziprasidone (20 to 60 mg 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 IV hydration and electrolyte replacement [23].

**3.3.9.B.12] Paresthesia**

a) Incidence: up to 2% [1]

b) Paresthesia was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

**3.3.9.B.13] Seizure**

a) Incidence: 0.4% [1]

b) Seizures were reported in 0.4% of ziprasidone-treated patients during clinical trials, although confounding factors may have contributed to the occurrence in many of these cases [1].

**3.3.9.B.14] Somnolence**

a) Incidence: 8% to 20% [1]

b) Somnolence was reported in 8%, 8%, and 20% of patients during short-term fixed-dose trials of IM ziprasidone mesylate 2 mg, 10 mg, and 20 mg, respectively [1].

### 3.3.9.B.15] Tardive dyskinesia

a) Incidence: rare [1]

b) The use of antipsychotic drugs, such as ziprasidone mesylate, is a risk factor for the development of tardive dyskinesia, potentially irreversible. The risk of developing the syndrome increases with duration of treatment and total cumulative dose. The incidence of the syndrome appears to be highest among the elderly, particularly women. However, any patient may be at risk to develop the syndrome, even after a comparatively brief treatment period at a low dose. Partial or complete resolution may occur with discontinuation of the antipsychotic drug. The smallest dose for the shortest duration should be the goal, with periodic treatment reassessment [1].

c) Tardive dyskinesia has been reported rarely as part of the postmarketing surveillance of ziprasidone hydrochloride [4].

## 3.3.10] Ophthalmic Effects

### 3.3.10.A] Ziprasidone Hydrochloride

#### 3.3.10.A.1] Abnormal vision

a) Incidence: 3% to 6% [4] [1]

b) The incidence of abnormal vision reported in short-term trials of patients with bipolar mania was 6% for ziprasidone hydrochloride-treated subjects (n=279) compared with 3% for placebo-treated patients (n=136) [4] [1].

c) In short-term trials, the incidence of abnormal vision was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) [4] [1].

d) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with schizophrenia revealed a dependent relationship between the development of abnormal vision and the dose of ziprasidone hydrochloride [4] [1].

#### 3.3.10.A.2] Oculogyric crisis

a) A case report describes a 28-year-old woman who experienced oculogyric crisis following administration of ziprasidone (80 mg/day) for the treatment of schizophrenia. At 15 years of age, the patient was diagnosed with schizophrenia and was treated with haloperidol with poor response. At the age of 24 years, the patient developed upward deviation of the eyes and blepharospasm for 2 hours which occurred 2 to 3 times per week. She had no loss of consciousness, visual hallucinations, torticollis, or opisthotonus. Haloperidol was switched to ziprasidone 80 mg/day with no further occurrences for the next 7 months. However, this movement returned with a frequency of up to 3 episodes per month while on ziprasidone. An EEG revealed no epileptic issues. Clonazepam (1 mg/day) was then initiated with significant improvement in movement disorder, and she remained free of oculogyric crisis for 8 months. Three days upon discontinuation of clonazepam, movement disorder returned [45].

b) Oculogyric crisis developed in an 11-year-old boy after receiving ziprasidone 20 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 [46].

### 3.3.12] Psychiatric Effects

#### 3.3.12.A] Ziprasidone Hydrochloride

##### 3.3.12.A.1] Mania

###### a) Summary

1) There have been several case reports of mania/hypomania associated ziprasidone use, including rare reports during postmarketing use [4] [1] [49] [50].

###### b) Incidence: rare [4] [39]

c) Hypomania developed in a 40-year-old man on 2 occasions following the initiation and reinitiation of ziprasidone therapy for the treatment bipolar schizoaffective disorder. Hypomania developed 8 days after ziprasidone (100 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 8 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 [49].

d) Four cases of mania related to the initiation of ziprasidone administration have been reported in bipolar patients. Three of the cases occurred in men who were 25, 26, and 45 years of age and the other case occurred in a 29-year-old woman. In each case, the patient was receiving multiple psychotropic medications prior to ziprasidone administration. Each patient received an initial ziprasidone dose of 20 mg twice a day. Manic symptoms occurred within 3 to 7 days in each of the male patients at this dosage. With the female 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 patients' 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 [50].

#### 3.3.12.B] Ziprasidone Mesylate

##### 3.3.12.B.1] Agitation

a) Incidence: up to 2% [1]

b) Agitation was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

##### 3.3.12.B.2] Personality disorder

a) Incidence: up to 2% [1]

b) Personality disorder was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

### 3.3.14] Reproductive Effects

#### 3.3.14.A] Ziprasidone Hydrochloride

##### 3.3.14.A.1] Orgasm disorder

a) A 50-year-old woman experienced spontaneous orgasms following initiation of ziprasidone treatment. The patient had not been sexually active for the past 10 years and had been suffering from symptoms of prolonged depression, decreased need for sleep, racing thoughts, rapid speech, increased goal-directed activities, and suicidal ideation. Following medication trials and evaluation, a diagnosis of bipolar II disorder was confirmed. A mood-stabilizing agent, oral ziprasidone 20 mg twice daily, was initiated. Within 1 week, she experienced abrupt onset sexual arousal and spontaneous orgasms 10 to 15 times daily, and each episode lasted for approximately 30 seconds to 1 minute. Extrapyramidal symptoms, specifically mild torticollis, also progressed over the following 3 days. Upon feeling a sensation of swollen tongue and throat which did not obstruct breathing, she sought emergency medical attention. Ziprasidone was discontinued. Her extrapyramidal symptoms resolved within 1 day and spontaneous orgasms resolved within 3 days. At follow-up, oxcarbazepine was initiated which was effective and well tolerated by the patient [51].

#### 3.3.14.A.2] Priapism

a) Incidence: rare [4] [1]

b) Although no causal relationship has been established, rare postmarketing reports of priapism with ziprasidone use have been observed and 1 case was reported during premarketing trials. Surgical intervention may be required in severe cases [4] [1].

c) An African American man developed priapism on 2 occasions after receiving risperidone and again after receiving ziprasidone for the treatment of schizophrenia. Following risperidone treatment (4 mg twice daily), the man developed an erection lasting 13 hours, which resolved upon irrigation of the corpora with phenylephrine 200 mcg. 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 [52].

### 3.3.14.B] Ziprasidone Mesylate

#### 3.3.14.B.1] Dysmenorrhea

a) Incidence: up to 2% [1]

b) Dysmenorrhea was reported in up to 2% of patients during short-term fixed-dose trials of IM ziprasidone mesylate [1].

#### 3.3.14.B.2] Priapism

a) Incidence: up to 1% [1]

b) Priapism, reported in up to 1% of patients during short-term fixed-dose trials of IM ziprasidone mesylate, has also been observed during postmarketing use. Surgical intervention may be required in severe cases [1].

### 3.3.15] Respiratory Effects

#### 3.3.15.A] Ziprasidone Hydrochloride

##### 3.3.15.A.1] Cough

a) Incidence: 3% [4] [1]

b) In short-term trials, the incidence of increased cough was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 1% for placebo-treated subjects (n=273) [4] [1].

### 3.3.15.A.2] Dyspnea

- a) Incidence: 1% to 2% [4] [1]
- b) The incidence of dyspnea reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) [4] [1].
- c) Dyspnea was frequently observed (at least 1 in 100) in patients who received oral ziprasidone hydrochloride at multiple doses greater than 4 mg/day during premarketing schizophrenia clinical trials (n=3834) [4] [1].

### 3.3.15.A.3] Pharyngitis

- a) Incidence: 3% [4] [1]
- b) The incidence of pharyngitis reported in short-term trials of patients with bipolar mania was 3% for ziprasidone hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) [4] [1].

### 3.3.15.A.4] Pulmonary embolism

- a) The use of ziprasidone was associated with an increased risk of pulmonary embolism (PE; adjusted odds ratio [OR] 1.21; 95% CI, 1.07 to 1.38; p=0.003) in a retrospective epidemiologic analysis of 2006 data from a clinical and economic United States hospital database (Premier's Perspective). Hospitalized adult patients with at least 1 prescription for an antipsychotic drug and a diagnosis of PE were evaluated, and the analysis was adjusted for age, sex, components of the Charlson comorbidity index, hospital inpatient or outpatient status, and diagnoses of infection, sepsis, inflammatory bowel disease, and psychotic disorders. Among the total population of adults identified (n=28,723,771), 0.3% of patients were hospitalized with a PE (76,814 events); however, among the patients using antipsychotics (n=450,951), 0.83% of patients presented with a PE (3764 events) for an adjusted OR of 1.17 (95% CI, 1.13 to 1.21; p less than 0.001). Although PE risk varied by specific antipsychotic, the first- and second-generation antipsychotics demonstrated comparable risk with an adjusted OR of 1.19 (95% CI, 1.13 to 1.25; p less than 0.001) and 1.15 (95% CI, 1.09 to 1.21; p less than 0.001), respectively, and higher doses corresponded to an increased risk. Limitations of the analysis include lack of data for risk factors or previous episodes of venous thromboembolism (eg, deep vein thrombosis), non-hospital prescriptions, compliance with prescriptions, and proof of causality between antipsychotic use and a PE based on a temporal sequence. A review of the patient characteristics also revealed more patients using antipsychotics (36.7%) had a grade 2 or higher Charlson comorbidity index when compared with nonusers (11.9%) which suggests a poorer state of health at baseline [32].

### 3.3.15.A.5] Respiratory tract infection

- a) Incidence: 8% [4] [1]
- b) In short-term trials, the incidence of respiratory tract infection was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 3% for placebo-treated subjects (n=273) [4] [1].

### 3.3.15.A.6] Rhinitis

- a) Incidence: 4% [4] [1]
- b) In short-term trials, the incidence of rhinitis was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) compared with 2% for placebo-treated subjects (n=273) [4] [1].

c) An analysis of 4 short-term, fixed-dose, placebo-controlled studies of patients with [schizophrenia](#) revealed a dependent relationship between the development of [rhinitis](#) and the dose of [ziprasidone](#) hydrochloride [4] [1].

### 3.3.15.B] [Ziprasidone](#) Mesylate

#### 3.3.15.B.1] [Pulmonary embolism](#)

a) The use of [ziprasidone](#) was associated with an increased risk of [pulmonary embolism](#) (PE; adjusted odds ratio [OR] 1.21; 95% CI, 1.07 to 1.38; p=0.003) in a retrospective epidemiologic analysis of 2006 data from a clinical and economic United States hospital database (Premier's Perspective). Hospitalized adult patients with at least 1 prescription for an antipsychotic drug and a diagnosis of PE were evaluated, and the analysis was adjusted for age, sex, components of the Charlson comorbidity index, hospital inpatient or outpatient status, and diagnoses of infection, sepsis, [inflammatory bowel disease](#), and [psychotic disorders](#). Among the total population of adults identified (n=28,723,771), 0.3% of patients were hospitalized with a PE (76,814 events); however, among the patients using antipsychotics (n=450,951), 0.83% of patients presented with a PE (3764 events) for an adjusted OR of 1.17 (95% CI, 1.13 to 1.21; p less than 0.001). Although PE risk varied by specific antipsychotic, the first- and second-generation antipsychotics demonstrated comparable risk with an adjusted OR of 1.19 (95% CI, 1.13 to 1.25; p less than 0.001) and 1.15 (95% CI, 1.09 to 1.21; p less than 0.001), respectively, and higher doses corresponded to an increased risk. Limitations of the analysis include lack of data for risk factors or previous episodes of [venous thromboembolism](#) (eg, [deep vein thrombosis](#)), non-hospital prescriptions, compliance with prescriptions, and proof of causality between antipsychotic use and a PE based on a temporal sequence. A review of the patient characteristics also revealed more patients using antipsychotics (36.7%) had a grade 2 or higher Charlson comorbidity index when compared with nonusers (11.9%) which suggests a poorer state of health at baseline [32].

### 3.3.16] Other

#### 3.3.16.A] [Ziprasidone](#) Hydrochloride

##### 3.3.16.A.1] [Accidental injury](#)

a) Incidence: 4% [4] [1]

b) The incidence of accidental injuries reported in short-term trials of patients with bipolar mania was 4% for [ziprasidone](#) hydrochloride-treated subjects (n=279) compared with 1% for placebo-treated patients (n=136) [4] [1].

c) In short-term trials, the incidence of accidental injuries was 4% among [ziprasidone](#) hydrochloride-treated [schizophrenia](#) subjects (n=702) compared with 2% for placebo-treated subjects (n=273) [4] [1].

##### 3.3.16.A.2] [Death](#)

a) Results of a population-based, retrospective, cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years or older) with [dementia](#). Pair-wise comparisons were made between atypical and no antipsychotic use and conventional and atypical antipsychotic use. A total of 27,259 matched pairs were identified and the [dementia](#) cohort was stratified based on place of residence (community vs long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in



the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio [HR], 1.31; 95% CI, 1.02 to 1.7); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55; 95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both, 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined [34].

**b)** Results of a population-based, retrospective, cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years or older) compared with atypical antipsychotic medications. The analysis excluded patients with [cancer](#) and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% CI, 1.39 to 1.56). In the multivariable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional compared with atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with [risperidone](#), the mortality ratio associated with [haloperidol](#) was 2.14 (95% CI, 1.86 to 2.45) and [loxapine](#) was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with [olanzapine](#). The increased mortality risk for conventional compared with atypical drug therapy was greatest when higher (above median) doses were used (mortality ratio, 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio, 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multivariable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study [35].

**c)** 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 (RR) 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, 1.3 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 1.9). 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 [54].

### 3.3.16.A.3] [Serotonin syndrome](#)

a) A 50-year-old woman with [schizophrenia](#) developed [serotonin-syndrome](#) 4 hours after receiving her second dose of [ziprasidone](#) 40 mg. Fourteen days prior to receiving [ziprasidone](#), she had been admitted to the hospital with agitation, auditory hallucinations, and delusions of persecution. She was initiated on [quetiapine](#) 400 mg/day, [valproate](#) sodium 1000 mg/day, and [lorazepam](#) 4 mg/day. On day 9, she had fluctuating consciousness, and a laboratory workup revealed an increase in total [valproic acid](#) at 167 mcg/mL (normal range, 50 to 100 mcg/mL) and free [valproic acid](#) at 27 mcg/mL (normal range, 5 to 10 mcg/mL), with all other laboratory values normal. All medications were discontinued. Consciousness returned 4 days later; however, all her original psychotic symptoms remained. [Ziprasidone](#) was initiated and 4 hours following her second 40 mg dose, she became severely restless, agitated, and disoriented to time and place. Physical examination revealed [hypertension](#), [tachycardia](#), hyperhidrosis, hyperreflexia, ataxia, and flushing. Her body temperature was 35.8 C, and she showed no focal neurological signs or rigidity. [Ziprasidone](#) was discontinued and all symptoms, including disorientation, subsided within 24 hours. [Quetiapine](#) 600 mg/day was initiated and the patient was discharged 8 days later with no further psychotic symptoms. A diagnosis of full-blown [serotonin syndrome](#) was made based on the Sternbach criteria [53].

### 3.3.16.B| [Ziprasidone](#) Mesylate

#### 3.3.16.B.1| Death

a) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years or older) with [dementia](#). Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the [dementia](#) cohort was stratified based on place of residence (community vs long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio [HR], 1.31; 95% CI, 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55; 95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both, 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined [34].

b) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years or older) compared with atypical antipsychotic medications. The analysis excluded patients with [cancer](#) and included only new users of antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% CI, 1.39 to 1.56). In the multivariable analysis which controlled for potential confounders, the adjusted



mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with [risperidone](#), the mortality ratio associated with [haloperidol](#) was 2.14 (95% CI, 1.86 to 2.45) and [loxapine](#) was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with [olanzapine](#). The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multivariable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study [35].

### 3.4] [Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

#### A) [Teratogenicity/Effects in Pregnancy](#)

##### 1) U.S. Food and Drug Administration's Pregnancy Category: Category C (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](#).

##### 2) Australian Drug Evaluation Committee's (ADEC) Category: B3

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

##### 3) Crosses Placenta: Unknown

##### 4) Clinical Management

a) There are no adequate and well-controlled studies of [ziprasidone](#) use during pregnancy in humans; however, animal studies have shown developmental toxicity with potential [teratogenic effects](#) with [ziprasidone](#) administration. In humans, third-trimester antipsychotic drug exposure has been associated with extrapyramidal and/or withdrawal symptoms in neonates. Therefore, [ziprasidone](#) should be used during pregnancy only if the maternal benefit justifies the fetal risk [56].

##### 5) Literature Reports

a) There are no adequate and well-controlled studies of [ziprasidone](#) use in pregnant women. Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care [56].

b) Developmental toxicity, including possible [teratogenic effects](#), was reported in animal studies. An increased incidence of fetal structural abnormalities ([ventricular septal defects](#) and

other cardiovascular malformations and kidney changes) were observed in rabbits administered ziprasidone doses of 30 mg/kg/day (3 times the maximum recommended human dose (MRHD) on a mg/m(2) basis) during organogenesis. In rats, embryofetal toxicity (ie, decreased fetal weights, delayed skeletal ossification) was observed following ziprasidone doses up to 160 mg/kg/day (8 times the MRHD on a mg/m(2) basis), but no evidence of teratogenicity was noted [56].

## B) Breastfeeding

### 1) Micromedex 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 in human milk; therefore, breastfeeding in women who are receiving ziprasidone is not recommended [56].

## 3.5] Drug Interactions

### 3.5.1] Drug-Drug Combinations

#### 3.5.1.A] Acarbose

1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia

2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

#### 3.5.1.B] Albiglutide

1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia

2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using

antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.C] Alfuzosin

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.D] Almotriptan

1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.E] Alogliptin

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.F] Amifampridine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#) [101].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#) [101].
- 7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.G] Amineptine

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.H] Amiodarone

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.I] 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 [76] [77].
- 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) [75].

### 3.5.1.J] Amitriptyline

1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.K] Amitriptylinoxide

1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.L] Amoxapine

1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.M] [Amphetamine](#)

1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.N] [Anagrelide](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

#### 3.5.1.O] [Apomorphine](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

#### 3.5.1.P] [Aripiprazole](#)

1) Interaction Effect: increased risk of QT-interval prolongation

- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.Q] Arsenic Trioxide

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.R] Artemether

- 1) Interaction Effect: an increased risk of QT-interval prolongation
- 2) Summary: Coadministration of ziprasidone with other drugs known to prolong the QT interval, such as artemether/lumefantrine, is contraindicated due to the potential for additive effects on QT-interval prolongation [56]. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [82].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of ziprasidone with other drugs known to prolong the QT interval, such as artemether/lumefantrine, is contraindicated due to the potential for additive effects on QT-interval prolongation [56]. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [82].
- 7) Probable Mechanism: additive effects on QT-interval prolongation

### 3.5.1.S] Asenapine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified



- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.T] Astemizole

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.U] Atazanavir

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.V] Azithromycin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.W] Bedaquiline

- 1) Interaction Effect: increased risk of QT-interval prolongation



- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.X] Bepridil

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of bepridil with drugs that cause QT-interval prolongation is contraindicated [105], as coadministration may increase the risk of ventricular arrhythmias.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of bepridil with drugs that cause QT-interval prolongation is contraindicated [105], as coadministration may increase the risk of ventricular arrhythmias.
- 7) Probable Mechanism: additive QT-interval prolongation

#### 3.5.1.Y] Bromocriptine

- 1) Interaction Effect: decreased bromocriptine efficacy
- 2) Summary: Ziprasidone is a dopamine antagonist and bromocriptine is a potent dopamine receptor agonist. The coadministration of bromocriptine with ziprasidone may decrease bromocriptine efficacy [70] [1]. The concomitant use of bromocriptine and ziprasidone should be undertaken with caution.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone, a dopamine antagonist [1], and bromocriptine, a potent dopamine receptor agonist, may result in decreased bromocriptine efficacy [70] and should be undertaken with caution.
- 7) Probable Mechanism: antagonism at dopamine receptors

#### 3.5.1.Z] Brompheniramine

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.AA] Buserelin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.AB] Buspirone**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.AC] Canagliflozin**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

**3.5.1.AD] Carbamazepine**

- 1) Interaction Effect: decreased [ziprasidone](#) plasma concentrations and increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: Ziprasidone is metabolized primarily by CYP3A4. Coadministration with carbamazepine (a CYP3A4 inducer) 200 mg twice daily for 21 days decreased the ziprasidone AUC by approximately 35%. With higher doses of carbamazepine, the effect may be greater. Therefore, caution should be used when carbamazepine and ziprasidone are coadministered due to the potential for reduced ziprasidone plasma concentrations. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug, such as carbamazepine, may increase the risk for serotonin syndrome.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of carbamazepine, a CYP3A4 inducer, with ziprasidone, a CYP3A4 substrate. Concomitant use of carbamazepine and ziprasidone may result in decreased ziprasidone plasma concentrations. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug, such as carbamazepine, may increase the risk for serotonin syndrome.

7) Probable Mechanism: Induction of CYP3A4-mediated ziprasidone metabolism by carbamazepine; additive serotonergic effects

### 3.5.1.AE] Ceritinib

1) Interaction Effect: increased exposure of CYP3A substrate

2) Summary: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate [69].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate [69].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of drug by ceritinib

### 3.5.1.AF] Chloroquine

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.AG] Chlorpheniramine

1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.AH] [Chlorpromazine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.AI] [Chlorpropamide](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.AJ] [Ciprofloxacin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.AK] Cisapride

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of cisapride with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [91].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of cisapride with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [91].

7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.AL] Citalopram

1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.AM] Clarithromycin

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

**3.5.1.AN] Clomipramine**

- 1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

**3.5.1.AO] Clonidine**

- 1) Interaction Effect: induction or exacerbation of orthostatic regulation disturbances
- 2) Summary: [Ziprasidone](#) is a neuroleptic agent that may induce orthostatic hypotension associated with dizziness, [tachycardia](#), and syncope due to its alpha-blocking activity, especially when first initiated [56]. The coadministration of [clonidine](#) with [ziprasidone](#) may result in orthostatic regulation disturbance induction or exacerbation [83] [84] and should be approached with particular caution [56].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [clonidine](#) and neuroleptics, such as [ziprasidone](#) [56], may induce or exacerbate orthostatic regulation disturbances (eg, dizziness, fatigue, orthostatic hypotension) [83] [84] and should be approached with particular caution [56].
- 7) Probable Mechanism: unknown

**3.5.1.AP] Clozapine**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.AQ] Cocaine**



- 1)) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2)) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7)) Probable Mechanism: Additive serotonergic effect

### 3.5.1.AR] Crizotinib

- 1)) Interaction Effect: increased risk of QT prolongation; increased [ziprasidone](#) exposure
- 2)) Summary: Coadministration of [ziprasidone](#) with other drugs that prolong the QT interval, such as crizotinib [85], is contraindicated due to the potential for additive effects on the QT prolongation and an increased risk of [torsade de pointes](#) [56]. Additionally, the concurrent use of crizotinib, a moderate CYP3A4 inhibitor, with a drug that is predominantly metabolized by CYP3A4, such as [ziprasidone](#), may result in increased [ziprasidone](#) exposure [85].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [ziprasidone](#) with other drugs that prolong the QT interval, such as crizotinib [85], is contraindicated due to the potential for [torsade de pointes](#) [56]. Additionally, the concurrent use of crizotinib, a moderate CYP3A4 inhibitor, with a drug that is predominantly metabolized by CYP3A4, such as [ziprasidone](#), may result in increased [ziprasidone](#) exposure [85].
- 7)) Probable Mechanism: additive effects on QT interval; inhibition of CYP3A-mediated [ziprasidone](#) metabolism by crizotinib
- 8)) Literature Reports

a)) In a QT prolongation study, [ziprasidone](#) and [haloperidol](#) were evaluated in a direct comparison study in patient volunteers. The mean QTc change from baseline was 4.6 msec following the first [ziprasidone](#) 20 mg injection and 12.8 msec following the second 30 mg injection. The mean increase in QTc from baseline for [haloperidol](#) was 6 msec following the first 7.5 mg injection and 14.7 msec following the second 10 mg injection. In this study, no patients had a QTc interval exceeding 500 msec [56].

### 3.5.1.AS] Cyclobenzaprine

- 1)) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2)) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.AT] Dabrafenib

1) Interaction Effect: decreased exposure of CYP3A4 substrate and increased risk of QT-interval prolongation

2) Summary: Dabrafenib is a CYP3A4 inducer associated with QT prolongation. While concurrent use of dabrafenib with a CYP3A4 substrate may decrease the exposure of the substrate [89], coadministration of dabrafenib with a CYP3A4 substrate that also prolongs the QT interval may result in additive QT-prolongation effects and increase the risk of ventricular arrhythmias. The use of dabrafenib with certain drugs that prolong the QT interval is contraindicated [67].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of dabrafenib with drugs that cause QT-interval prolongation may result in additive effects on the QT interval, and may increase the risk of ventricular arrhythmias. The use of dabrafenib with certain drugs that prolong the QT interval is contraindicated [67].

7) Probable Mechanism: induction of CYP3A4-mediated metabolism by dabrafenib; additive QT-interval prolongation

### 3.5.1.AU] Dapagliflozin

1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia

2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

### 3.5.1.AV] Darunavir

1) Interaction Effect: increased CYP3A substrate exposure

2) Summary: Use caution with coadministration of darunavir (a CYP3A inhibitor) with CYP3A substrates. Coadministration may increase CYP3A substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. If coadministered, monitor for adverse reactions associated with concomitant drugs [90].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical



6J) Clinical Management: Use caution with coadministration of [darunavir](#) (a CYP3A inhibitor) with CYP3A substrates. Coadministration may increase CYP3A substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. Monitor for adverse reactions associated with concomitant drugs if coadministered [90].

7J) Probable Mechanism: inhibition of CYP3A substrate metabolism

### 3.5.1.AW] [Dasatinib](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7J) Probable Mechanism: additive QT interval effects

### 3.5.1.AX] [Deferasirox](#)

1J) Interaction Effect: reduced plasma concentrations of CYP3A4 substrate

2J) Summary: Concomitant use of [deferasirox](#), a CYP3A4 inducer, and drugs that are metabolized by CYP3A4 may lead to decreased CYP3A4 substrate concentrations. Concomitant use [midazolam](#), a CYP3A4 substrate, and [deferasirox](#) resulted in decreases in the [midazolam](#) C<sub>max</sub> and AUC by 23% and 17%, respectively, in healthy volunteers. In the clinical setting, this effect may be more pronounced. Therefore, caution should be used when [deferasirox](#) is coadministered with other CYP3A4 substrates. If concomitant use is required, monitor patients for reduced effectiveness [88].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [deferasirox](#) and a CYP3A4 substrate such as escitalopram, [imatinib](#), and [tacrolimus](#), may result in decreased CYP3A4 substrate plasma concentrations. Therefore, caution is advised when [deferasirox](#) and drugs metabolized by CYP3A4 are coadministered and monitoring of patients for reduced effectiveness is recommended [88].

7J) Probable Mechanism: induction of CYP3A4-mediated metabolism by [deferasirox](#)

### 3.5.1.AY] [Degarelix](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.

7J) Probable Mechanism: additive effects on the QT interval

### 3.5.1.AZ] Delamanid

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7J) Probable Mechanism: additive QT interval effects

### 3.5.1.BA] Desipramine

1J) Interaction Effect: increased risk of QT-interval prolongation and increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2J) Summary: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7J) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.BB] Deslorelin

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.

7J) Probable Mechanism: additive effects on the QT interval

**3.5.1.BC] Desvenlafaxine**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.BD] Dextroamphetamine**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.BE] Dextromethorphan**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.BF] Dibenzepin**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.BG] [Disopyramide](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.BH] [Dofetilide](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.BI] [Dolasetron](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7J) Probable Mechanism: additive QT interval effects

### 3.5.1.BJ] Domperidone

1J) Interaction Effect: increased risk of QT prolongation

2J) Summary: Coadministration of domperidone and ziprasidone is contraindicated [56]. Coadministration may increase the risk of serious cardiac events, including ventricular arrhythmias and sudden cardiac death. Case-control studies demonstrated an association of serious ventricular arrhythmias and sudden cardiac death, particularly with domperidone doses greater than 30 mg/day and use of domperidone in patients older than 60 years [109].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of domperidone and ziprasidone is contraindicated [56] as this may increase the risk of serious cardiac effects, including ventricular arrhythmias and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years [109].

7J) Probable Mechanism: additive effects on QT interval prolongation

### 3.5.1.BK] Doxepin

1J) Interaction Effect: increased risk of QT-interval prolongation and increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2J) Summary: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7J) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.BL] Dronedaronone

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [67].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of dronedarone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [67].

7J) Probable Mechanism: additive QT-interval prolongation

**3.5.1.BM] Droperidol**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.BN] Dulaglutide**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].
- 7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

**3.5.1.BO] Duloxetine**

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.BP] Ebastine**

- 1) Interaction Effect: increased risk of QT-interval prolongation

- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.BQ| Eletriptan

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.BR| Empagliflozin

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hyperglycemia [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hyperglycemia [72].
- 7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

### 3.5.1.BS| Eribulin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical



6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.BT] Erythromycin

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.BU] Escitalopram

1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.BV] Eslicarbazepine Acetate

1) Interaction Effect: decreased exposure of CYP3A4 substrates

2) Summary: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [68], use caution and monitor the patient closely.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [68], use caution and monitor the patient closely.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism by eslicarbazepine acetate



**3.5.1.BW] Exenatide**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

**3.5.1.BX] Famotidine**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.BY] Felbamate**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.BZ] Fentanyl**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.CA] Fingolimod

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.CB] Flecainide

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.CC] Fluconazole

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7J) Probable Mechanism: additive QT interval effects

### 3.5.1.CD| Fluoxetine

1J) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

7J) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.CE| Fluvoxamine

1J) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7J) Probable Mechanism: Additive serotonergic effect

### 3.5.1.CF| Formoterol

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7J) Probable Mechanism: additive QT interval effects

**3.5.1.CG| Foscarnet**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.CH| Fosphenytoin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.CI| Frovatriptan**

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.CJ| Furazolidone**

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.CK] [Galantamine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.CL] [Gatifloxacin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.CM] [Gemifloxacin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.CN] Glimepiride**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

**3.5.1.CO] Glipizide**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

**3.5.1.CP] Glyburide**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

**3.5.1.CQ] Gonadorelin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.CR| [Goserelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

#### 3.5.1.CS| [Granisetron](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.CT| [Halofantrine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical



6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.CU] Haloperidol

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.CV] Histrelin

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.CW] Hydromorphone

1) Interaction Effect: an increase in CNS or respiratory depression

2) Summary: The concomitant use of HYDROmorphone and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including respiratory depression, hypotension, profound sedation, and coma. When administering HYDROmorphone and an antipsychotic together, dose reduction of one or both of the medications should be considered [64].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of HYDROmorphone and other CNS depressants, such as antipsychotics, may result in respiratory depression, hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered [64].

7) Probable Mechanism: additive effects

### 3.5.1.CX] Hydroquinidine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.CY| Hydroxychloroquine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Hydroxychloroquine has been associated with QT interval prolongation [65] [66], ventricular premature contractions, and torsade de pointes [66]. Coadministration of other QT-interval prolonging drugs is contraindicated, as life-threatening additive effects on the QT interval, including torsades de pointes, may occur [67].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Hydroxychloroquine has been associated with QT interval prolongation [65] [66], ventricular premature contractions, and torsade de pointes [66]. Coadministration of other QT-interval prolonging drugs is contraindicated, as life-threatening additive effects on the QT interval, including torsades de pointes, may occur [67].
- 7) Probable Mechanism: additive QT interval effects
- 8) Literature Reports

a) Hydroxychloroquine-associated QT interval prolongation was reported in a 41-year-old woman with congestive heart failure with systolic left ventricular dysfunction. Her comorbidities included hypertension, systemic lupus erythematosus, and stage 5 chronic kidney disease. One week after reinitiation of hydroxychloroquine therapy, a significant prolongation of the QT interval (QTc 614 msec) was observed during a routine ECG. Following treatment discontinuation of hydroxychloroquine, serial ECGs demonstrated a shortening of the QTc interval. The patient's QTc was 473 msec at a follow up 1 year after discharge [65].

b) QT prolongation and refractory ventricular arrhythmia were reported with chronic hydroxychloroquine use in a 67-year-old woman with systemic lupus erythematosus. The patient had been receiving prednisolone, theophylline, and hydroxychloroquine 200 mg/day for 1 year. The patient had a medical history of cirrhosis, hepatitis B virus related hepatoma with portal vein thrombosis, and asthma. The patient experienced a sudden episode of unconsciousness and generalized rigidity while at home. Although the patient regained consciousness within minutes and had no complaints of chest pain, palpitation, limb weakness, incontinence, or confusion, the episode recurred several times. Upon admission the ECG showed multiple ventricular premature contractions, torsade de pointes, and prolongation of the QT interval. Treatment with hydroxychloroquine was discontinued. Following medical management, ventricular arrhythmia subsided after 4 days and the QT interval shortened [66].

### 3.5.1.CZ| Hydroxytryptophan

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.DA] [Ibutilide](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.DB] [Idelalisib](#)

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) Summary: Avoid coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects. During a drug interaction study, coadministration of idelalisib and [midazolam](#) (CYP3A substrate) resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax [103].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate should be avoided, as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects [103].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by idelalisib
- 8) Literature Reports

a) During a drug interaction study, administration of idelalisib 150 mg for 15 doses followed by a single dose of [midazolam](#) 5 mg (a CYP3A substrate) in healthy volunteers, resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax [103].

#### 3.5.1.DC] [Iloperidone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation

- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.DD] Imipramine

- 1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.
- 7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.DE] Insulin

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].
- 7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

### 3.5.1.DF] Insulin Aspart, Recombinant

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor

glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.DG| [Insulin](#) Bovine

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.DH| [Insulin](#) Degludec

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.DI| [Insulin](#) Detemir

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

#### 3.5.1.DJ] [Insulin Glulisine](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

#### 3.5.1.DK] [Insulin Lispro, Recombinant](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

#### 3.5.1.DL] [Iproniazid](#)

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical



6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.DM] [Isocarboxazid](#)

1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.DN] [Itraconazole](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

#### 3.5.1.DO] [Ivabradine](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

#### 3.5.1.DP] [Ketoconazole](#)

1) Interaction Effect: increased risk of QT-interval prolongation



- 2)) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7)) Probable Mechanism: additive QT interval effects

### 3.5.1.DQ| Lapatinib

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7)) Probable Mechanism: additive QT interval effects

### 3.5.1.DR| Leuprolide

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7)) Probable Mechanism: additive effects on the QT interval

### 3.5.1.DS| Levofloxacin

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.DT] Levomilnacipran

1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.DU] Linagliptin

1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia

2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

### 3.5.1.DV] Linezolid

1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

**3.5.1.DW] Liraglutide**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

**3.5.1.DX] Lithium**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.DY] Lixisenatide**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hyperglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

**3.5.1.DZ] Lofepamine**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.EA] Lorcaserin

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.EB] Lumefantrine

- 1) Interaction Effect: an increased risk of QT-interval prolongation
- 2) Summary: Coadministration of [ziprasidone](#) with other drugs known to prolong the QT interval, such as artemether/lumefantrine, is contraindicated due to the potential for additive effects on QT-interval prolongation [56]. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [82].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [ziprasidone](#) with other drugs known to prolong the QT interval, such as artemether/lumefantrine, is contraindicated due to the potential for additive effects on QT-interval prolongation [56]. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy, due to the long half-life of lumefantrine (3 to 6 days) [82].
- 7) Probable Mechanism: additive effects on QT-interval prolongation

#### 3.5.1.EC] Mefloquine

- 1) Interaction Effect: increased risk of QT-interval prolongation

- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.ED] Melitracen

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.EE] Meperidine

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.EF] Mesoridazine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of mesoridazine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [110].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: established

6) Clinical Management: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [110].

7) Probable Mechanism: additive QT-interval prolongation

### 3.5.1.EG] [Metformin](#)

1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)

2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.EH] [Methadone](#)

1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.EI] [Methylene Blue](#)

1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical



6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.EJ] [Metoclopramide](#)

1) Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)

2) Summary: Concomitant use of [metoclopramide](#) with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated [58]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions. Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [59].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [metoclopramide](#) with antipsychotic agents is contraindicated [58]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [59].

7) Probable Mechanism: unknown

### 3.5.1.EK] [Metronidazole](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.EL] [Mifepristone](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Both [mifepristone](#) and [ziprasidone](#) prolong the QTc interval in a dose-related manner [55] [56]. The coadministration of [ziprasidone](#) and drugs that prolong the QT interval, such as [mifepristone](#), should be avoided [56] due to the potential for additive effects on QT interval prolongation and an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#)). Due to the long half-life of [mifepristone](#), wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [ziprasidone](#). However, if concomitant use is necessary, use the lowest effective dose possible and monitor closely for QT interval prolongation; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing the [ziprasidone](#) dose [55].



- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant administration of ziprasidone and drugs that prolong the QT interval, such as mifepristone [55], due to the potential for additive effects on QT interval prolongation and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) [56]. Due to the long half-life of mifepristone, wait at least 2 weeks after stopping mifepristone (Korlym(TM)) before initiating ziprasidone. However, if concomitant use is necessary, use the lowest effective dose possible and monitor closely for QT interval prolongation; additionally, wait at least 2 weeks after stopping mifepristone (Korlym(TM)) before increasing the ziprasidone dose [55].
- 7) Probable Mechanism: additive effects of QT interval prolongation

### 3.5.1.EM] Miglitol

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].
- 7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

### 3.5.1.EN] Milnacipran

- 1) Interaction Effect: increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Concomitant use of milnacipran and an antipsychotic may result in hypertension, coronary artery vasoconstriction or serotonin syndrome, which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of serotonin syndrome develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated [86].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of milnacipran and an antipsychotic may result in hypertension and coronary artery vasoconstriction through additive serotonergic effects. Therefore, use caution when coadministering these agents. If symptoms of serotonin syndrome develop, discontinue treatment immediately and institute the appropriate supportive symptomatic treatment [86].
- 7) Probable Mechanism: additive serotonergic effect

### 3.5.1.EO] Mirtazapine

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.EP] [Mitotane](#)

1) Interaction Effect: decreased exposure of CYP3A4 substrates

2) Summary: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [104] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [104] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism by [mitotane](#)

### 3.5.1.EQ] [Mizolastine](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.ER] [Moclobemide](#)

1) Interaction Effect: increased risk for [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.ES] [Moxifloxacin](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.ET] [Nafarelin](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.

7) Probable Mechanism: additive effects on the QT interval

### 3.5.1.EU] [Naratriptan](#)

1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.EV] [Nateglinide](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.EW] Nefazodone

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.EX] Nelfinavir

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.EY] Netupitant

- 1) Interaction Effect: increased exposure of CYP3A4 substrate
- 2) Summary: Caution is advised with the coadministration of netupitant (a CYP3A inhibitor) and a CYP3A substrate, as this may increase plasma concentrations of the CYP3A substrate due to inhibition of CYP3A4-mediated metabolism by netupitant and increase the risk of adverse effects that may persist for days. Examples of CYP3A substrates include IV administered chemotherapeutic agents and benzodiazepines; close monitoring is recommended of the increased adverse effects of these agents [60].

- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised with the coadministration of netupitant (a CYP3A inhibitor) and a CYP3A substrate, as this may increase plasma concentrations of the CYP3A substrate and increase the risk of adverse effects that may persist for days. Examples of CYP3A substrates include IV administered chemotherapeutic agents and benzodiazepines; close monitoring is recommended of the increased adverse effects of these agents [60].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by netupitant
- 8) Literature Reports
  - a) **Pharmacokinetic studies** demonstrated that coadministration of netupitant 300 mg/**palonosetron** 0.5 mg and **docetaxel**, a chemotherapeutic agents metabolized by CYP3A4, increased **docetaxel** Cmax by 49% and AUC by 35%, compared with coadministration with **palonosetron** alone. Additionally, coadministration with another chemotherapeutic agent, **etoposide**, increased **etoposide** Cmax and AUC by 10% and 28%, respectively. After a single oral dose of the benzodiazepine **midazolam** 7.5 mg was coadministered with netupitant 300 mg, mean Cmax and AUC of **midazolam** was 36% and 126% higher, respectively [60].

### 3.5.1.EZ] Nialamide

- 1) Interaction Effect: increased risk for **serotonin syndrome** (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: **Serotonin syndrome** has been reported with **ziprasidone** monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for **serotonin syndrome**. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: **Serotonin syndrome** has been reported with **ziprasidone** monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for **serotonin syndrome**. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.FA] Nilotinib

- 1) Interaction Effect: additive QT interval prolongation; increased **ziprasidone** exposure
- 2) Summary: Coadministration of nilotinib (a moderate CYP3A4 inhibitor) [74], with **ziprasidone** (a CYP3A4 substrate) is contraindicated. Both drugs are known to prolong the QT interval, and concurrent use may increase the risk of additive QT interval-prolonging effects [18].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of **ziprasidone** with drugs that prolong the QT interval, such as nilotinib [74], is contraindicated [18].
- 7) Probable Mechanism: additive effects on QT interval prolongation; inhibition of CYP3A4-mediated **ziprasidone** metabolism
- 8) Literature Reports

- a) Although not specifically studied with the CYP3A4 substrate [ziprasidone](#) [18], multiple doses of nilotinib (a moderate CYP3A4 inhibitor) increased the systemic exposure of [midazolam](#) (a CYP3A4 substrate) by 2.6-fold in patients with [chronic myeloid leukemia](#) [74].

### 3.5.1.FB| [Norfloxacin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.FC| [Nortriptyline](#)

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.FD| [Octreotide](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.FE| [Ofloxacin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation

- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.FF] Olanzapine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.FG] Ondansetron

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.FH] Opipramol

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical



6J) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7J) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.FI] [Paliperidone](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7J) Probable Mechanism: additive QT interval effects

#### 3.5.1.FJ] [Panobinostat](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7J) Probable Mechanism: additive QT interval effects

#### 3.5.1.FK] [Paroxetine](#)

1J) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).

7J) Probable Mechanism: additive QT interval effects; additive serotonergic effect

**3.5.1.FL] Pasireotide**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.FM] Pazopanib**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.FN] Pentamidine**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.FO] Pentazocine**

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.FP| Perflutren Lipid Microsphere

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.FQ| Perphenazine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.FR| Phenelzine

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.FS] Pimozide**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [107].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [107].
- 7) Probable Mechanism: additive QT-interval prolongation

**3.5.1.FT] Pioglitazone**

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

**3.5.1.FU] Pipamperone**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.FV] Piperazine**

- 1) Interaction Effect: increased exposure of CYP3A4 substrates and increased risk of QT-interval prolongation
- 2) Summary: Concomitant administration of piperazine and QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of

QT-interval prolonging drugs, that may still be circulating at the time of piperazine administration, is contraindicated. Concurrent administration of piperazine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperazine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperazine therapy [102].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of piperazine (a QT-interval prolonging drug) with other QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperazine administration, is contraindicated. Concurrent administration of piperazine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperazine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperazine therapy [102].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by piperazine; additive QT-interval prolongation

### 3.5.1.FW] Posaconazole

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.FX] Pramlintide

1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia

2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

### 3.5.1.FY] Primidone

1) Interaction Effect: decreased exposure of CYP3A4 substrates

2) Summary: [Primidone](#) is metabolized to [phenobarbital](#) [57] (a strong CYP3A4 inducer). Concomitant use of [primidone](#) with certain CYP3A4 substrates may result in decreased exposure of the CYP3A4 substrate and should be avoided if clinically possible. If concomitant administration is required, use caution and monitor the patient closely.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use if clinically possible. If coadministration is required, use caution and monitor the patient closely.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism by [primidone](#)

### 3.5.1.FZ] [Probucol](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.GA] [Procainamide](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.GB] [Procarbazine](#)

1) Interaction Effect: increased risk for [serotonin syndrome](#) (hypertension, hyperthermia, myoclonus, mental status changes)

2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.GC] [Prochlorperazine](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

#### 3.5.1.GD] [Promethazine](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

#### 3.5.1.GE] [Propafenone](#)

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7) Probable Mechanism: additive QT interval effects

#### 3.5.1.GF] [Protriptyline](#)

1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)



2)) Summary: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7)) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.GG| Quetiapine

1)) Interaction Effect: increased risk of QT-interval prolongation

2)) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7)) Probable Mechanism: additive QT interval effects

### 3.5.1.GH| Quinidine

1)) Interaction Effect: increased risk of QT-interval prolongation

2)) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7)) Probable Mechanism: additive QT interval effects

### 3.5.1.GI| Quinine

1)) Interaction Effect: increased risk of QT-interval prolongation

2)) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3)) Severity: contraindicated

4)) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.GJ] Ranolazine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.GK] Rasagiline

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.GL] Repaglinide

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].
- 7) Probable Mechanism: hyperglycemia induced by antipsychotic agent

**3.5.1.GM] Rilpivirine**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.GN] Risperidone**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.GO] Ritonavir**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.GP] Rizatriptan**

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.GQ| [Rosiglitazone](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.GR| [Saqinavir](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.GS| [Saxagliptin](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].

7J) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.GT] [Selegiline](#)

1J) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7J) Probable Mechanism: Additive serotonergic effect

### 3.5.1.GU] [Sertindole](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].

7J) Probable Mechanism: additive QT interval effects

### 3.5.1.GV] [Sertraline](#)

1J) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2J) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.

7J) Probable Mechanism: Additive serotonergic effect

### 3.5.1.GW] [Sevoflurane](#)

1J) Interaction Effect: increased risk of QT-interval prolongation

- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.GX] Sibutramine

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.GY] Siltuximab

- 1) Interaction Effect: decreased effectiveness of CYP3A4 substrate
- 2) Summary: Coadministration of siltuximab and a CYP3A4 substrate may result in increased metabolism and decreased effectiveness of the substrate. Approach concurrent use with caution. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation [100]. If coadministration is required, monitoring and dose adjustments may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of siltuximab and a CYP3A4 substrate may increase the metabolism of the substrate and decrease its effectiveness. Use caution when coadministering siltuximab and a CYP3A4 substrate. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation [100]. If coadministration is required, monitoring and dose adjustments may be warranted.
- 7) Probable Mechanism: inhibition of interleukin-6 by siltuximab increases CYP450 levels leading to increased metabolism of CYP450 substrates

### 3.5.1.GZ] Sitagliptin

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

#### 3.5.1.HA| [Sodium Phosphate](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.HB| [Sodium Phosphate, Dibasic](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.HC| [Sodium Phosphate, Monobasic](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects



**3.5.1.HD] Solifenacin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.HE] Sorafenib**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.HF] Sotalol**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.HG] Sparfloxacin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of sparfloxacin with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [108].
- 3) Severity: contraindicated
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [sparfloxacin](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [108].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.HH] St John's Wort

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.HI] 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 [96] [97] [98] [99].
- 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 [92] [93] [94].

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) [95].

#### 3.5.1.HJ] Sumatriptan

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.HK] [Sunitinib](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.HL] [Tacrolimus](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.HM] [Tamoxifen](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

#### 3.5.1.HN] [Tapentadol](#)

- 1)) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2)) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7)) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.HO| Telaprevir

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7)) Probable Mechanism: additive QT interval effects

#### 3.5.1.HP| Telavancin

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7)) Probable Mechanism: additive QT interval effects

#### 3.5.1.HQ| Telithromycin

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.HR] Terfenadine

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of terfenadine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [106].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of terfenadine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [106].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.HS] Tetrabenazine

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.HT] Thioridazine

1) Interaction Effect: increased risk of QT-interval prolongation

2) Summary: The concomitant use of thioridazine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [87].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of thioridazine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [87].

7) Probable Mechanism: additive QT interval effects

### 3.5.1.HU] Tianepetine

1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.HV] [Tizanidine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.HW] [Tolazamide](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.HX] [Tolbutamide](#)

- 1) Interaction Effect: decreased glucose-lowering effects; increased risk of [hyperglycemia](#)
- 2) Summary: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of [hyperglycemia](#), which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for [hypoglycemia](#) [72].
- 7) Probable Mechanism: [hyperglycemia](#) induced by antipsychotic agent

### 3.5.1.HY] [Tolterodine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.HZ] [Toremifene](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#) [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.IA] [Tramadol](#)

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.IB] [Tranylcypromine](#)



- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

### 3.5.1.IC] [Trazodone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.ID] [Trimipramine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [ziprasidone](#) with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. [Serotonin syndrome](#) has also been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for [serotonin syndrome](#).
- 7) Probable Mechanism: additive QT interval effects; additive serotonergic effect

**3.5.1.IE] Triptorelin**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval [61] [62] [63], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

**3.5.1.IF] Tryptophan**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.IG] Valproic Acid**

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

**3.5.1.IH] Vandetanib**

- 1) Interaction Effect: increased risk of QT-interval prolongation

- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.II] Vardenafil

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.IJ] Vemurafenib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

### 3.5.1.IK] Venlafaxine

- 1) Interaction Effect: increased risk of QT-interval prolongation and increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6J) Clinical Management: The concomitant use of ziprasidone with other drugs that prolong the QT interval is contraindicated because coadministration may result in additive risk for QT-interval prolongation. Serotonin syndrome has also been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase the risk for serotonin syndrome.

7J) Probable Mechanism: additive QT interval effects; additive serotonergic effect

### 3.5.1.IL] Vilanterol

1J) Interaction Effect: increased risk of QT-interval prolongation

2J) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].

7J) Probable Mechanism: additive QT interval effects

### 3.5.1.IM] Vilazodone

1J) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)

2J) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.

7J) Probable Mechanism: Additive serotonergic effect

### 3.5.1.IN] Vildagliptin

1J) Interaction Effect: decreased glucose-lowering effects; increased risk of hyperglycemia

2J) Summary: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Atypical antipsychotic agents are associated with an increased risk of hyperglycemia, which can sometimes be severe [71]. Glycemic control may worsen in patients using antidiabetic agents. Monitor glucose levels more closely [72] and adjust antidiabetic agent doses as necessary [73]. Upon withdrawal of the atypical antipsychotic, monitor for hypoglycemia [72].

7J) Probable Mechanism: hyperglycemia induced by antipsychotic agent

**3.5.1.IO] Vinflunine**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.IP] Voriconazole**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.IQ] Vorinostat**

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of ziprasidone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias [33] [48].
- 7) Probable Mechanism: additive QT interval effects

**3.5.1.IR] Vortioxetine**

- 1) Interaction Effect: increased risk for serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes)
- 2) Summary: Serotonin syndrome has been reported with ziprasidone monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for serotonin syndrome. Therefore, exercise caution with concomitant use.
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.IS] [Zolmitriptan](#)

- 1) Interaction Effect: increased risk for [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)
- 2) Summary: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Serotonin syndrome](#) has been reported with [ziprasidone](#) monotherapy and in combination with other serotonergic drugs [48] [33]; coadministration with another serotonergic drug may increase risk for [serotonin syndrome](#). Therefore, exercise caution with concomitant use.
- 7) Probable Mechanism: Additive serotonergic effect

#### 3.5.1.IT] [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 [80] [81].
- 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) [78].

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](#) [79].

## 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 in signs and symptoms of schizophrenia or manic or mixed episodes associated with bipolar disorder are indicative of efficacy.

##### 2) Toxic

###### a) Laboratory Parameters

1) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below [121]:

a) Measure fasting plasma glucose at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of diabetes. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control [121].

b) Measure fasting lipid profile at baseline, at week 12, and then every 5 years thereafter. Repeat testing should be done more frequently as clinically indicated [121].

2) Perform CBC [56] [4] with differential frequently during the first few months of therapy in patients with preexisting low WBC or a history of drug-induced leukopenia or neutropenia.

3) Serum potassium and magnesium levels should be performed at baseline and periodically, especially in patients prone to electrolyte disturbances [56] [4].

###### b) Physical Findings

1) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below [121]:

a) Obtain personal and family history of obesity, diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease prior to treatment and review annually with patient [121].



**b)** Track weight and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter [121].

**c)** Measure waist circumference at baseline and annually thereafter [121].

**d)** Measure blood pressure at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of hypertension [121].

**2)** Examine patient for tardive dyskinesia before initiation and then annually. Patients at high risk for tardive dyskinesia (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects) should be examined every 6 months throughout the duration of treatment [122].

**3)** Closely monitor patients for suicidality during therapy due to the increased risk of suicide attempts in patients with schizophrenia or bipolar disorder [56] [4].

## **B)** Ziprasidone Mesylate

### **1)** Therapeutic

#### **a)** Physical Findings

**1)** Reduction of acute agitation in schizophrenia patients is indicative of efficacy.

### **2)** Toxic

#### **a)** Laboratory Parameters

**1)** Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below [121]:

**a)** Measure fasting plasma glucose at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of diabetes. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control [121].

**b)** Measure fasting lipid profile at baseline, at week 12, and then every 5 years thereafter. Repeat testing should be done more frequently as clinically indicated [121].

**2)** Perform CBC [56] with differential frequently during the first few months of therapy in patients with a history of a clinically significant low WBC or drug-induced leukopenia or neutropenia.

**3)** [56]

**4j)** Serum potassium and magnesium levels should be performed at baseline, and periodically, especially in patients prone to electrolyte disturbances [56].

**bj) Physical Findings**

**1j)** Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic monitoring for obesity and diabetes, as listed below [121]:

**aj)** Obtain personal and family history of obesity, diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease, prior to treatment and review annually with patient [121].

**bj)** Track weight and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter [121].

**cj)** Measure waist circumference at baseline, and annually thereafter [121].

**dj)** Measure blood pressure at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of hypertension [121].

**2j)** Examine patient for tardive dyskinesia before initiation and then annually. Patients at higher risk for tardive dyskinesia (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects) should be examined every 6 months throughout the duration of treatment [122].

**3j)** Monitor orthostatic vital signs, especially during the initial dose-titration period, in the elderly, in patients with renal or hepatic impairment, in patients predisposed to hypotension, including those with dehydration and hypovolemia, or known cerebrovascular disease, or cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities) [56]

**4j)** Closely monitor patients for suicidality during therapy due to the increased risk of suicide attempts in patients with schizophrenia [56].

## **4.2j Patient Instructions**

### **Aj) Ziprasidone (By mouth)**

#### **Ziprasidone**

Treats [schizophrenia](#) and [bipolar disorder](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction](#) to [ziprasidone](#), if you have a history of QT prolongation (heart rhythm problem), or if you had a recent [heart attack](#).

How to Use This Medicine:

Capsule

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

It is best to take this medicine with food at the same time every day.

Swallow the capsule whole. Do not break, crush, or chew it.

Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

#### Drugs and Foods to Avoid:

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

Do not use this medicine together with [amiodarone](#), [arsenic trioxide](#), [chlorpromazine](#), [disopyramide](#), [dofetilide](#), [dolasetron](#) mesylate, [droperidol](#), [gatifloxacin](#), [halofantrine](#), [levomethadyl acetate](#), [mefloquine](#), [mesoridazine](#), [moxifloxacin](#), [pentamidine](#), [pimozide](#), [probucol](#), [procainamide](#), [quinidine](#), [sotalol](#), [sparfloxacin](#), [tacrolimus](#), or [thioridazine](#).

Some medicines can affect how [ziprasidone](#) works. Tell your doctor if you are using any of the following:

[Carbamazepine](#), [ketoconazole](#), [levodopa](#)

Blood pressure medicines

Diuretics (water pill)

#### Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have liver disease, blood or bone marrow problems, [diabetes](#), high cholesterol, or a history of seizures or [breast cancer](#). Tell your doctor if you have heart rhythm problems or any heart or blood vessel problems, including low blood pressure, [heart failure](#), or a history of a [heart attack](#).

This medicine may cause the following problems:

Heart rhythm problems

[Neuroleptic malignant syndrome](#) (possibly life-threatening [neurological disorder](#))

Drug reaction with [eosinophilia](#) and systemic symptoms (DRESS), which can damage organs such as the liver, kidney, or heart

[Tardive dyskinesia](#) (trouble controlling muscle movements)

This medicine may make you dizzy or drowsy. Do not drive or do anything else that could be dangerous until you know how this medicine affects you. Stand or sit up slowly if you feel lightheaded or dizzy.

You may get overheated more easily while you are using this medicine. Use caution when you exercise strenuously or are outside in hot weather. Drink plenty of water to stay hydrated.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

#### 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

Chills, [cough](#), sore throat, body aches

Fast, slow, pounding, or uneven heartbeat

Fever, skin rash, or swollen glands in your armpits, neck, or groin  
Fever, sweating, confusion, muscle stiffness, seizures  
Increased thirst, hunger, or urination  
Lightheadedness, dizziness, fainting  
Painful, prolonged erection of your penis  
Twitching or muscle movements you cannot control (especially in your face, tongue, or jaw)  
Unusual bleeding, bruising, or weakness

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

Sleepiness, tiredness  
Stuffy or runny 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 agitation in patients with [schizophrenia](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. You should not receive it if you had an [allergic reaction](#) to [ziprasidone](#), if you have a history of QT prolongation (heart rhythm problem), or if you had a recent [heart attack](#).

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 health provider 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.

Do not use this medicine together with [amiodarone](#), [arsenic trioxide](#), [chlorpromazine](#), [disopyramide](#), [dofetilide](#), [dolasetron](#) mesylate, [droperidol](#), [gatifloxacin](#), [halofantrine](#), [levomethadyl acetate](#), [mefloquine](#), [mesoridazine](#), [moxifloxacin](#), [pentamidine](#), [pimozide](#), [probucol](#), [procainamide](#), [quinidine](#), [sotalol](#), [sparfloxacin](#), [tacrolimus](#), or [thioridazine](#).

Some medicines can affect how [ziprasidone](#) works. Tell your doctor if you are using any of the following:

[Carbamazepine](#), [ketoconazole](#), [levodopa](#)

Blood pressure medicines

Diuretics (water pills)

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [kidney disease](#), blood or bone marrow problems, [diabetes](#), high cholesterol, or a history of seizures or [breast cancer](#). Tell your doctor if you have heart rhythm problems or any heart or blood vessel problems, including low blood pressure, [heart failure](#), or history of a [heart attack](#).

This medicine may cause the following problems:

Heart rhythm problems

[Neuroleptic malignant syndrome](#) (possibly life-threatening [neurological disorder](#))

Drug reaction with [eosinophilia](#) and systemic symptoms (DRESS), which can damage organs such as the liver, kidney, or heart

**Tardive dyskinesia** (trouble controlling muscle movements)

This medicine may make you dizzy or drowsy. Do not drive or do anything else that could be dangerous until you know how this medicine affects you. Stand or sit up slowly if you feel lightheaded or dizzy.

You may get overheated more easily while you are using this medicine. Use caution when you exercise strenuously or are outside in hot weather. Drink plenty of water to stay hydrated.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. 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

Chills, **cough**, sore throat, body aches

Fast, slow, pounding, or uneven heartbeat

Fever, skin rash, or swollen glands in your armpits, neck, or groin

Fever, sweating, confusion, muscle stiffness, seizures

Increased thirst, hunger, or urination

Lightheadedness, dizziness, fainting

Painful, prolonged erection of your penis

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

Unusual bleeding, bruising, or weakness

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

Headache, nausea

Pain where the shot was given

Sleepiness, tiredness

Weight gain

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

**4.3] Place In Therapy**

**A)** Current users of atypical antipsychotic drugs (including **ziprasidone**) and typical antipsychotic drugs had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular **tachyarrhythmia**. Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses were defined as comparable to less than 100 milligrams (mg) of **chlorpromazine**, and doses comparable to **chlorpromazine** 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In atypical antipsychotic use, the incidence rate ratio increased from 1.59 (95% CI, 1.03 to 2.46) in low-dose use to 2.86 (95% CI, 2.25 to 3.65) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis [123]. In an editorial in The New England Journal of Medicine, it has been suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before

and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation [124].

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

**C)** 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) Ziprasidone Hydrochloride

###### 1) Mechanism of Action

**a)** The exact mechanism of action of ziprasidone hydrochloride is unknown; however, it is proposed that ziprasidone exerts action as a psychotropic agent for schizophrenia by antagonism of dopamine type 2 and serotonin type 2 receptors. The activity of ziprasidone is primarily through the parent drug and unchanged ziprasidone represents about 44% of total drug-related material in the serum. The exact mechanism in bipolar disorder is unknown. In vitro, ziprasidone demonstrated high binding affinity for dopamine D2 and D3, serotonin 5HT2A, 5HT2C, 5HT1A, 5HT1D, and alpha(1)-adrenergic receptors. Moderate binding affinity to the histamine H1 receptor was also demonstrated. Some side effects of ziprasidone may be explained by antagonistic effects at 5HT2, histamine H1 (somnolence), and alpha(1)-adrenergic (orthostatic hypotension) receptors [56].

##### B) Ziprasidone Mesylate

###### 1) Mechanism of Action

**a)** The exact mechanism of action of ziprasidone hydrochloride is unknown; however, it is proposed that ziprasidone exerts action as a psychotropic agent for schizophrenia by antagonism of dopamine type 2 and serotonin type 2 receptors. The activity of ziprasidone is primarily through the parent drug and unchanged ziprasidone represents about 44% of total drug-related material in the serum. The exact mechanism in bipolar disorder is unknown. In vitro, ziprasidone demonstrated high binding affinity for dopamine D2 and D3, serotonin 5HT2A, 5HT2C, 5HT1A, 5HT1D, and alpha(1)-adrenergic receptors. Moderate binding affinity to the histamine H1 receptor was also demonstrated. Some side effects of ziprasidone may be explained by antagonistic effects at 5HT2, histamine H1 (somnolence), and alpha(1)-adrenergic (orthostatic hypotension) receptors [56].

#### 4.5] Therapeutic Uses

##### 4.5.A] Ziprasidone Hydrochloride

###### 4.5.A.1] Bipolar I disorder, Acute manic or mixed episodes, monotherapy

###### 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 as monotherapy for the treatment of acute manic or mixed episodes in patients with [bipolar disorder](#), with or without psychotic features [4] [1] [5]

**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 [5].

**4.5.A.2] Bipolar I disorder, to [lithium](#) or [valproate](#); Adjunct**

FDA Labeled Indication

**a) Overview**

FDA Approval: Adult, yes; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

**b) Summary:**

Indicated for the maintenance treatment of bipolar I disorder, as an adjunct to [lithium](#) or [valproate](#) [1]

**c) Adult:**



1j) As adjunctive therapy to [lithium](#) or [valproate](#) in the treatment of bipolar I disorder, [ziprasidone](#) (n=127) was superior to placebo (n=112) in increasing the time to recurrence of a mood episode (depressive, manic, or mixed) in a placebo-controlled trial of patients who met DSM-IV criteria for bipolar I disorder. Eligible patients were required to be stabilized on [ziprasidone](#) plus [lithium](#) or [valproate](#) for at least 8 weeks prior to randomization. The primary endpoint was time to recurrence of a mood episode requiring clinical intervention, including discontinuation of treatment, initiation of medication or hospitalization, or a Mania Rating Scale score 18 or higher or a MADRS (Montgomery-Asberg Depression Rating Scale) score of 18 or higher on 2 consecutive assessments within 10 days [1].

#### 4.5.A.3] [Dementia](#)

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF [DEMENTIA](#)

#### 4.5.A.4] [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](#) [14].

##### c) Adult:

1j) 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 [14].

#### 4.5.A.5] [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:**

[Ziprasidone](#) has been associated with positive and negative symptom improvement with relatively low incidence of extrapyramidal symptoms [6] [7] [8] [9] [10].

Clinical trials have demonstrated that [ziprasidone](#) decreases the rate of [relapse](#) in patients with chronic, stable [schizophrenia](#) [4] [11] [1].

Patients with acute exacerbation of [schizophrenia](#) or [schizoaffective disorder](#) receiving [ziprasidone](#) had significant improvement in positive, negative, and depressive symptoms within one week compared with placebo [12] [13].

**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 [11].

**2)** In a double-blind, randomized, placebo-controlled trial, patients with acute exacerbation of [schizophrenia](#) or [schizoaffective disorder](#) receiving [ziprasidone](#) had significant improvement in positive, negative, and depressive symptoms within one week compared with placebo. Patients were randomized to [ziprasidone](#) 80 milligrams (mg) per day (n=106, mean age 36.8 years old), [ziprasidone](#) 160 mg per day (n=104, mean age 35.8 years old) or placebo (n=92, mean age 37.2 years old) for 6 weeks. All patients presented with baseline Positive and Negative Syndrome Scale (PANSS) scores of at least 60 (mean of 98.2, 95.8 and 97.3 in the 80-mg, 180-mg, and placebo groups, respectively), and remained hospitalized for the first 14 days of the study. Depressive symptoms were present at baseline in 50% of all patients per Montgomery Asberg Depression Rating Scale (MADRS). PANSS, Brief Psychiatric Rating Scale, Clinical Global Impression-Improvement, and Positive and Negative Syndrome Scale-Negative scores decreased significantly in each of the [ziprasidone](#) groups compared with placebo (p=0.05). [Ziprasidone](#) patients identified with depressive symptoms at baseline had significant improvement in MADRS scores (p=0.05). All differences became apparent at week 1, and were maintained at week 6. Extrapyramidal symptoms were reported in 1% of placebo patients, 2% of [ziprasidone](#) 80 mg patients, and 7% of [ziprasidone](#) 160 mg patients [12].

3j) In a case series of 196 inpatients with acute exacerbation of [schizophrenia](#) or [schizoaffective disorder](#), [ziprasidone](#) significantly reduced symptoms within one week of initiation. Patients (mean age 38.4 years old, 60.1% male) were moderately ill at baseline, with mean Brief Psychiatric Rating Scale (BPRS) score of 58.3 and mean Clinical Global Impression-Severity (CGI-S) score of 5.3. Mean initial [ziprasidone](#) dose was 136.9 milligrams (mg) per day; at discharge the mean dose was 186.3 mg per day, and at that point 75% of patients were taking at least 160 mg per day, with 45% of patients taking a dose above 160 mg per day. Response to treatment, defined as at least 30% reduction in ratings scores, was noted in 74% (95% confidence interval (CI), 68% to 80%) of patients via BPRS criteria, and 67% (95% CI, 61% to 74%) of patients via CGI-S score at hospital discharge (average length of stay 23.4 days). Effects became statistically significant compared with baseline at week one, and persisted throughout follow-up. Daily doses between 120 mg per day and 240 mg per day were associated with greater likelihood of response compared with doses below 120 mg per day (odds ratio, 3.7; 95% CI, 1.5 to 8.8). Common side effects were sedation (16.3%), somnolence (7.1%), restlessness (6.1%), [akathisia](#) (4.1%), insomnia (3.1%), anxiety (2.5%), tremor (2.6%) and [parkinsonism](#) (1%); no events were considered severe [13].

4j) [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 [4] [1].

#### 4.5.Bj [Ziprasidone Mesylate](#)

##### 4.5.B.1j 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](#) mesylate is effective for the treatment of acute agitation in schizophrenic patients [1]

In an open-label three-day study (n=21), intramuscular (IM) [ziprasidone](#) significantly improved mean Brief Psychiatric Rating Scale (BPRS) and Behavioral Activity Rating Scale (BARS) scores from baseline in elderly patients with schizophrenia-related acute psychotic agitation [2]

###### c) Adult:

1j) The efficacy of intramuscular [ziprasidone](#) mesylate 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 [1].

2) In an open-label three-day study (n=21), intramuscular (IM) ziprasidone significantly improved mean Brief Psychiatric Rating Scale (BPRS) and Behavioral Activity Rating Scale (BARS) scores from baseline in elderly patients with schizophrenia-related acute psychotic agitation. Patients (mean age, 71.4 +/- 1.3 years (yr); range, 60 to 81 yr) hospitalized with acute psychosis related to schizophrenia (diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria) were eligible for enrollment. Concomitant use of other psychotropic medications was not permitted. Following hospitalization and screening procedures (1 to 6 hours), patients received three days of flexible-dose IM ziprasidone (10 or 20 mg initially, followed by 10 to 20 mg every 12 hours as needed; not to exceed 40 mg per day). After three days of ziprasidone therapy, the mean BPRS score significantly decreased by 26.8 points from 76.9 +/- 2.4 points at baseline to 50.1 +/- 1.9 points at study completion (p=0.001). Additionally, the mean BARS score (measure of agitation) decreased from 5.8 +/- 0.16 points at baseline to 2.14 points after the 6th injection at study completion (p=0.001). Reported adverse events included acute urinary retention (1 patient), blurred vision (1 patient), and sedation (1 patient) [2].

#### 4.6] Comparative Efficacy / Evaluation With Other Therapies

##### 4.6.A] Aripiprazole

###### 1) Adverse Effects

a) In a 52-week, randomized study of outpatient adults with first-episode schizophrenia (N=254; mean age 26.4 years), metabolic syndrome occurred in 15.5% treated with aripiprazole, 9% treated with ziprasidone, and 8% treated with paliperidone extended-release. Mean daily treatment doses at week 52 were aripiprazole 14.5 mg, paliperidone 6.4 mg, and ziprasidone 28.4 mg. Aripiprazole significantly increased body weight (+3.1 kg), fasting blood glucose, and HbA1c compared with baseline values, and significantly more so than the other 2 treatment groups. LDL and triglycerides were significantly increased from baseline in both the paliperidone and aripiprazole groups and were significantly increased compared with ziprasidone. There were no changes in the ziprasidone group in glucose or lipid parameters, and no difference in waist circumference in any treatment group [135].

##### 4.6.B] Chlorpromazine

###### 4.6.B.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.C] Clozapine

###### 4.6.C.1] Schizophrenia

a) Ziprasidone was as effective as clozapine in the treatment of adults with schizophrenia resistant or intolerant to multiple cycles of antipsychotic therapy, according to an 18-week, randomized, double-blind,

flexible-dose, equivalence MOZART trial (Monitoring Oral Ziprasidone As Rescue Therapy; n=147). Patients diagnosed with DSM-IV schizophrenia and resistant or intolerant to 6 weeks of antipsychotic therapy, with baseline Clinical Global Impression Severity (CGI-S) scale score of at least 4, and a Positive and Negative Syndrome Scale (PANSS) score of at least 80 were included in the study. At baseline patients had a mean total PANSS score was 107 and CGI-S score of 5.2. Following a 1- to 7-day washout period and a 3-day placebo run-in period, patients were randomized to receive either ziprasidone (n=73) or clozapine (n=73). Ziprasidone therapy was initiated with 80 milligrams (mg)/day divided in 2 doses for 3 days, then flexibly dosed 80 to 160 mg/day. Clozapine was initiated with 25 mg/day titrated to 300 mg/day over 10 days, maintained for 1 week, then flexibly dosed 250 to 600 mg/day. Concomitant benzodiazepines, anticholinergic drugs, and propranolol was permitted. Clinical equivalence was defined as 13.5 points on the PANSS total score to yield an effect size of 0.45. The rate of premature discontinuation from the trial was similar in both groups (28 patients in each group (38.4%)) mainly due to adverse events. In an intent-to-treat analysis with last observation carried forward, the PANSS total score change from baseline was -25 +/- 22 (95% CI, -30.2 to -19.8) in ziprasidone-treated patients compared with -24.5 +/- 22.5 (95% CI, -29.7 to -19.2) in clozapine-treated patients, with no significant difference seen between treatment groups, yielding a baseline to endpoint effect size of 1.41 and 1.38, respectively. There were no significant differences between treatment groups in an analysis of subscale PANSS positive, negative, and general psychopathology, and in CGI-S score improvement. Treatment-emergent adverse events occurred in 71% (n=52) of ziprasidone-treated patients and in 79.5% (n=58) of clozapine-treated patients. There were significant decreases from baseline in median fasting total cholesterol, LDL-C, and triglycerides in ziprasidone-treated patients (p less than 0.05) [125].

#### 4.6.D] Haloperidol

##### 4.6.D.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 [129].

##### 4.6.D.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 [126].
- 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 [127]. 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 [128].

#### 4.6.E] Lurasidone Hydrochloride

##### 1) Adverse Effects

- a) Lurasidone and ziprasidone demonstrated similar safety and efficacy in the treatment of patients with chronic and stable schizophrenia or schizoaffective disorder (DSM-IV criteria) in a 3-week, double-blinded, fixed dose, parallel-group trial (n=307). Patients (age range, 18 to 65 years) discontinued prior medication, completed a 1 to 3 day placebo run-in period, and then were randomized to receive lurasidone 120 mg once daily (n=154) or ziprasidone 80 mg twice daily (n=153), all doses given with food. The primary outcome variables were safety measures, and the secondary outcome variables were efficacy endpoints, consisting of the Positive and Negative Syndrome Scale (PANSS) total score, and positive, negative, and general psychopathology subscale scores, the Clinical Global Impressions-Severity score (CGI-S), and the Calgary Depression Scale for Schizophrenia (CDSS). Discontinuation rates due to adverse effects for lurasidone and ziprasidone were 10.4% and 11.1%, respectively. Severe adverse effects occurred in 6.7% and 7.3% of patients treated with lurasidone and ziprasidone, respectively. Treatment with lurasidone and ziprasidone was not associated with significant baseline-to-endpoint or between-group differences on the Simpson-Angus Rating Scale, the Barnes Rating Scale, or the Abnormal Involuntary Movement Scale (AIMS). There were no significant differences in changes in weight, total cholesterol, triglycerides, glucose, HbA1C, or ECG abnormalities between the lurasidone and ziprasidone groups. In a last observation carried forward (LOCF) endpoint analysis of efficacy measures, improvement on the PANSS total and subscale scores, CGI-S, and CDSS total score was similar for lurasidone and ziprasidone [134].

#### 4.6.F] Olanzapine

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

a) In a secondary analysis of the randomized superiority CATIE study, [perphenazine](#) was noninferior to each of 3 second-generation antipsychotics with regards to Positive and Negative Syndrome Scale (PANSS) total score at 18 months (noninferiority margin, 6.3 PANSS points). The analysis included adults 18 to 65 years randomized to [perphenazine](#) (n=256), [olanzapine](#) (n=263), [quetiapine](#) (n=261), or [risperidone](#) (n=269); [ziprasidone](#) was not included in the analysis due to a small sample size [130].

b) 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 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 for [olanzapine](#). The time to discontinuation in the [olanzapine](#) group was significantly 37% longer compared with the [quetiapine](#) group and 25% longer compared with the [risperidone](#) group. Time to discontinuation due to adverse events was similar between all groups. More patients discontinued [olanzapine](#) due to greater weight gain (average of 0.9 kg/month) and greater increases in A1C, total cholesterol, and [triglycerides](#) [131].

#### 4.6.F.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) [132].

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 [133].

#### 4.6.G] Paliperidone

##### 1) Adverse Effects

a) In a 52-week, randomized study of outpatient adults with first-episode schizophrenia (N=254; mean age 26.4 years), metabolic syndrome occurred in 15.5% treated with aripiprazole, 9% treated with ziprasidone, and 8% treated with paliperidone extended-release. Mean daily treatment doses at week 52 were aripiprazole 14.5 mg, paliperidone 6.4 mg, and ziprasidone 28.4 mg. Aripiprazole significantly increased body weight (+3.1 kg), fasting blood glucose, and HbA1c compared with baseline values, and significantly more so than the other 2 treatment groups. LDL and triglycerides were significantly increased from baseline in both the paliperidone and aripiprazole groups and were significantly increased compared with ziprasidone. There were no changes in the ziprasidone group in glucose or lipid parameters, and no difference in waist circumference in any treatment group [135].

#### 4.6.H] Perphenazine

##### 4.6.H.1] Chronic schizophrenia

a) In a secondary analysis of the randomized superiority CATIE study, perphenazine was noninferior to each of 3 second-generation antipsychotics with regards to Positive and Negative Syndrome Scale (PANSS) total score at 18 months (noninferiority margin, 6.3 PANSS points). The analysis included adults 18 to 65 years randomized to perphenazine (n=256), olanzapine (n=263), quetiapine (n=261), or risperidone (n=269); ziprasidone was not included in the analysis due to a small sample size [130].

b) 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 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 for olanzapine. The time to discontinuation in the olanzapine group was significantly 37% longer compared with the quetiapine group and 25% longer compared with the risperidone group.

Time to discontinuation due to adverse events was similar between all groups. More patients discontinued [olanzapine](#) due to greater weight gain (average of 0.9 kg/month) and greater increases in A1C, total cholesterol, and [triglycerides](#) [131].

#### 4.6.I] Quetiapine

##### 4.6.I.1] Chronic schizophrenia

a) In a secondary analysis of the randomized superiority CATIE study, [perphenazine](#) was noninferior to each of 3 second-generation antipsychotics with regards to Positive and Negative Syndrome Scale (PANSS) total score at 18 months (noninferiority margin, 6.3 PANSS points). The analysis included adults 18 to 65 years randomized to [perphenazine](#) (n=256), [olanzapine](#) (n=263), [quetiapine](#) (n=261), or [risperidone](#) (n=269); [ziprasidone](#) was not included in the analysis due to a small sample size [130].

b) 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 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 for [olanzapine](#). The time to discontinuation in the [olanzapine](#) group was significantly 37% longer compared with the [quetiapine](#) group and 25% longer compared with the [risperidone](#) group. Time to discontinuation due to adverse events was similar between all groups. More patients discontinued [olanzapine](#) due to greater weight gain (average of 0.9 kg/month) and greater increases in A1C, total cholesterol, and [triglycerides](#) [131].

#### 4.6.J] Risperidone

##### 4.6.J.1] Chronic schizophrenia

a) In a secondary analysis of the randomized superiority CATIE study, [perphenazine](#) was noninferior to each of 3 second-generation antipsychotics with regards to Positive and Negative Syndrome Scale (PANSS) total score at 18 months (noninferiority margin, 6.3 PANSS points). The analysis included adults 18 to 65 years randomized to [perphenazine](#) (n=256), [olanzapine](#) (n=263), [quetiapine](#) (n=261), or [risperidone](#) (n=269); [ziprasidone](#) was not included in the analysis due to a small sample size [130].

b) 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 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 for [olanzapine](#). The time to discontinuation in the [olanzapine](#) group was significantly 37% longer compared with the [quetiapine](#) group and 25% longer compared with the [risperidone](#) group. Time to discontinuation due to adverse events was similar between all groups. More patients discontinued [olanzapine](#) due to greater weight gain (average of 0.9 kg/month) and greater increases in A1C, total cholesterol, and [triglycerides](#) [131].

## 6.0] References

- 1 Product Information: GEODON oral capsules, IM injection, ziprasidone HCl oral capsules, ziprasidone mesylate IM injection. Roerig, New York, NY, 2009.
- 2 Barak Y, Mazeh D, Plopski I, et al: Intramuscular ziprasidone treatment of acute psychotic agitation in elderly patients with schizophrenia. *Am J Geriatr Psychiatry* 2006; 14(7):629-633. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 3 Lesem MD, Zajecka JM, Swift RH, et al: Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry* 2001; 62:12-18.
- 4 Product Information: GEODON(R) oral suspension, ziprasidone hydrochloride oral suspension. Pfizer Inc., New York, NY, 2009.
- 5 Keck PE Jr, Versiani M, Potkin S, et al: Ziprasidone in the treatment of acute bipolar mania: A three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry* 2003; 160:741-748.
- 6 Reeves KR & Harrigan EP: The efficacy and safety of two fixed doses of ziprasidone in schizophrenia (abstract). *Eur Neuropsychopharmacol* 1996; 6(suppl):201.
- 7 Harrigan E, Morrissey M, & The Ziprasidone Working Group: The efficacy and safety of 28-day treatment with ziprasidone in schizophrenia/schizoaffective disorder (abstract). *Eur Neuropsychopharmacol* 1996; 6(suppl):200-201.
- 8 Citrome L: New antipsychotic medications: what advantages do they offer?. *Postgrad Med* 1997; 101:207-214.
- 9 Kerwin R & Taylor D: New antipsychotics: a review of their current status and clinical potential. *CNS Drugs* 1996; 6:71-82.
- 10 Anon: An expanding range of atypical antipsychotic agents to choose from (review). *Drugs Ther Perspect* 1996; 8:1-5.
- 11 Arato M, O'Connor R, & Meltzer HY: A 1-year, double-blind, placebo- controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the ziprasidone extended use in schizophrenia (zeus) study. *Int Clin Psychopharmacol* 2002; 17:207-215.
- 12 Daniel DG, Zimbroff DL, Potkin SG, et al: Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. *Neuropsychopharmacology* 1999; 20(5):491-505. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 13 Diaz-Marsa M, Sanchez S, & Rico-Villademoros F: Effectiveness and tolerability of oral ziprasidone in psychiatric inpatients with an acute exacerbation of schizophrenia or schizoaffective disorder: a multicenter, prospective, and naturalistic study. *J Clin Psychiatry* 2009; 70(4):509-517. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 14 Keck PE, Reeves KR, Harrigan EP, et al: Ziprasidone in the short term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. *J Clin Psychopharmacol* 2001; 21:27-35.
- 15 Everson G, Lasseter KC, Anderson KE, et al: The pharmacokinetics of ziprasidone in subjects with normal and impaired hepatic function. *Br J Clin Pharmacol* 2000; 49(suppl 1):21S-26S.
- 16 Aweeka F, Jayesekara D, Horton M, et al: The pharmacokinetics of ziprasidone in subjects with normal and impaired renal function. *Br J Clin Pharmacol* 2000; 49(suppl 1):27S-33S.
- 17 Wilner KD, Tensfeldt TG, Baris B, et al: Single- and multiple-dose pharmacokinetics of ziprasidone in healthy young and elderly volunteers. *Br J Clin Pharmacol* 2000; 49(suppl 1):15S-20S.
- 18 Product Information: GEODON(R) intramuscular injection, ziprasidone mesylate intramuscular injection. Roerig (per DailyMed), New York, NY, 2013.

- 19 US Food and Drug Administration (FDA): FDA Drug Safety Communication: FDA reporting mental health drug ziprasidone (Geodon) associated with rare but potentially fatal skin reactions. US Food and Drug Administration (FDA). Silver Spring, MD. 2014. Available from URL: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM426415.pdf>. As accessed 2014-12-11.
- 20 Product Information: GEODON(R) oral capsules, ziprasidone HCl oral capsules . Roerig (per DailyMed), New York, NY, 2013.
- 21 Product Information: GEODON(R) oral capsules, ziprasidone HCl oral capsules. Roerig (per FDA), New York, NY, 2013.
- 22 Anon: Anon: Food and drug administration center for drug evaluation and research psychopharmacologic drugs advisory committee.. Available at <http://www.fda.gov/OHRMS/DOCKETS/AC/00/transcripts/3619t1.rtf> (cited 12/2000), July 19, 2000.
- 23 Murty RG, Mistry SG, & Chacko RC: Neuroleptic malignant syndrome with ziprasidone (letter). *J Clin Psychopharmacol* 2002; 22(6):624-626.
- 24 Product Information: GEODON(R) intramuscular injection, ziprasidone mesylate intramuscular injection. Roerig (per FDA), New York, NY, 2013.
- 25 Product Information: GEODON(R) intramuscular injection, ziprasidone mesylate intramuscular injection. Roerig (per FDA), New York, NY, 2013.
- 26 Anon: An expanding range of atypical antipsychotic agents to choose from (review). *Drugs Ther Perspect* 1996; 8:1-5.
- 27 Kerwin R & Taylor D: New antipsychotics: a review of their current status and clinical potential. *CNS Drugs* 1996; 6:71-82.
- 28 Miceli JJ, Wilner KD, Hansen RA, et al: Single- and multiple-dose pharmacokinetics of ziprasidone under non- fasting conditions in healthy male volunteers. *Br J Clin Pharmacol* 2000; 49(suppl 1):5S-13S.
- 29 Goff DC, Posever R, Herz L, et al: An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 1998; 18(4):236-304.
- 30 Brown CS, Markowitz JS, Moore TR, et al: Atypical antipsychotics: part II. Adverse effects, drug interactions, and costs. *Ann Pharmacother* 1999; 33:210-217.
- 31 Citrome L: New antipsychotic medications: what advantages do they offer?. *Postgrad Med* 1997; 101:207-214.
- 32 Allenet B, Schmidlin S, Genty C, et al: Antipsychotic drugs and risk of pulmonary embolism. *Pharmacoepidemiol Drug Saf* 2012; 21(1):42-48. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 33 Product Information: GEODON(R) intramuscular injection, ziprasidone mesylate intramuscular injection. Roerig (per FDA), New York, NY, 2014.
- 34 Gill SS, Bronskill SE, Normand SL, et al: Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; 146(11):775-786. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 35 Schneeweiss S, Setoguchi S, Brookhart A, et al: Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ* 2007; 176(5):627-632. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 36 Snarr BS, Phan SV, Garner A, et al: Symptomatic bradycardia with oral aripiprazole and oral ziprasidone. *Ann Pharmacother* 2010; 44(4):760-763. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 37 Eker SS, Sarandol A, Akkaya C, et al: The potential relationship between QTc interval prolongation and ziprasidone treatment: three cases. *J Psychopharmacol* 2009; 23(8):993-996. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 38 Heinrich TW, Biblo LA, & Schneider J: Torsades de pointes associated with ziprasidone. *Psychosomatics* 2006; 47(3):264-268. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 39 Product Information: GEODON(R) oral capsules, IM injection, ziprasidone hcl oral capsules, ziprasidone mesylate IM injection. Pfizer, Inc, New York, NY, 2007.
- 40 Kutlu A, Dunder S, Altun NS, et al: Ziprasidone Induced Tardive Cervical Dystonia. *Psychopharmacol Bull* 2009; 42(4):64-68. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 41 Keck ME, Muller MB, Binder EB, et al: Ziprasidone-related tardive dyskinesia. *Am J Psychiatry* 2004; 161(1):175-176.
- 42 Letourneau G, Abdel-Baki A, Dubreucq S, et al: Hyperosmolar hyperglycemic state associated with ziprasidone treatment: a case report. *J Clin Psychopharmacol* 2011; 31(5):671-673. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 43 Product Information: GEODON(R) oral capsules, ziprasidone HCl oral capsules. Roerig (per FDA), New York, NY, 2013.
- 44 Raza S & Haq F: Ziprasidone-induced galactorrhea in an adolescent female: a case report. *Prim Care Companion J Clin Psychiatry* 2010; 12(3):1. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 45 Viana Bde M, Prais HA, Camargos ST, et al: Ziprasidone-related oculogyric crisis in an adult. *Clin Neurol Neurosurg* 2009; 111(10):883-885. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 46 Ramos AE, Shytle RD, Silver AA, et al: Ziprasidone-induced oculogyric crisis (letter). *J Am Acad Child Adolesc Psychiatry* 2003; 42(9):1013-1014.
- 47 Zaidi AN: Rhabdomyolysis after correction of hyponatremia in psychogenic polydipsia possibly complicated by ziprasidone. *Ann Pharmacother* 2005; 39:1726-1731.
- 48 Product Information: GEODON(R) oral capsules, ziprasidone HCl oral capsules. Roerig (per FDA), New York, NY, 2014.
- 49 Brieger P: Hypomanic episodes after receiving ziprasidone: an unintended "on-off-on" course of treatment. *J Clin Psychiatry* 2004; 65(1):132.
- 50 Baldassano CF, Ballas C, Datto SM, et al: Ziprasidone-associated mania: a case series and review of the mechanism. *Bipolar Disorders* 2003; 5:72-75.
- 51 Boora K, Chiappone K, Dubovsky S, et al: Ziprasidone-induced spontaneous orgasm. *J Psychopharmacol* 2010; 24(6):947-948. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 52 Reeves RR & Mack JE: Priapism associated with two atypical antipsychotic agents. *Pharmacotherapy* 2002; 22(8):1070-1073.
- 53 Lin PY, Hong CJ, & Tsai SJ: Serotonin syndrome caused by ziprasidone alone. *Psychiatry Clin Neurosci* 2010; 64(3):338-339. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 54 Wang PS, Schneeweiss S, Avorn J, et al: Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; 353:2335-2341.
- 55 Product Information: Korlym(TM) oral tablets, mifepristone oral tablets. Corcept Therapeutics (per manufacturer), Menlo Park, CA, 2012.
- 56 Product Information: GEODON(R) oral capsules, intramuscular injection, ziprasidone hcl oral capsules, intramuscular injection. Pfizer, Inc, New York, NY, 2010.
- 57 Product Information: Mysoline(R) oral tablets, primidone oral tablets. Valeant Pharmaceuticals North America (per DailyMed), Aliso Viejo, CA, 2010.

- 58 Product Information: REGLAN(R) oral tablets, metoclopramide oral tablets. Alaven Pharmaceutical LLC, Marietta, GA, 2009.
- 59 Product Information: METOZOLV ODT orally disintegrating tablets, metoclopramide hydrochloride orally disintegrating tablets. Salix Pharmaceuticals, Inc., Morrisville, NC, 2009.
- 60 Product Information: AKYNZEO(R) oral capsules, netupitant palonosetron oral capsules. Eisai Inc (per manufacturer), Woodcliff Lake, NJ, 2014.
- 61 Product Information: TRELSTAR(R) intramuscular injection suspension, triptorelin pamoate intramuscular injection suspension. Actavis Pharma, Inc. (per FDA), Parsippany, NJ, 2014.
- 62 Product Information: VANTAS(R) subcutaneous implant, histrelin acetate subcutaneous implant. Endo Pharmaceuticals Solutions Inc. (per DailyMed), Malvern, PA, 2014.
- 63 Product Information: LUPRON DEPOT intramuscular injection depot suspension, leuprolide acetate intramuscular injection depot suspension. AbbVie Inc. (per FDA), North Chicago, IL, 2014.
- 64 Product Information: EXALGO(R) extended release oral tablets, hydromorphone hydrochloride extended release oral tablets. ALZA Corporation, Vacaville, CA, 2010.
- 65 Morgan ND, Patel SV, & Dvorkina O: Suspected hydroxychloroquine-associated QT-interval prolongation in a patient with systemic lupus erythematosus. J Clin Rheumatol 2013; 19(5):286-288. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 66 Chen CY, Wang FL, & Lin CC: Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. Clin Toxicol (Phila) 2006; 44(2):173-175. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 67 Product Information: MULTAQ(R) oral tablets, dronedarone oral tablets. Sanofi-Aventis U.S. LLC (per FDA), Bridgewater, NJ, 2014.
- 68 Product Information: APTIOM(R) oral tablets, eslicarbazepine acetate oral tablets. Sunovion Pharmaceuticals, Inc. (per FDA), Marlborough, MA, 2013.
- 69 Product Information: ZYKADIA(TM) oral capsules, ceritinib oral capsules. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2014.
- 70 Product Information: Parlodel(R) oral tablets, oral capsules, bromocriptine mesylate oral tablets, oral capsules. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2012.
- 71 Product Information: LATUDA(TM) oral tablets, lurasidone HCl oral tablets. Sunovion Pharmaceuticals, Inc. (per manufacturer), Marlborough, MA, 2013.
- 72 Product Information: AMARYL(R) oral tablets, glimepiride oral tablets . Sanofi-Aventis U.S. LLC (per FDA), Bridgewater, NJ, 2013.
- 73 Product Information: TOUJEO(R) subcutaneous injection, insulin glargine subcutaneous injection. sanofi-aventis (per manufacturer), Bridgewater, NJ, 2015.
- 74 Product Information: TASIGNA(R) oral capsules, nilotinib oral capsules. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2014.
- 75 Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002.
- 76 Product Information: Solian(R), amisulpride tablets. Lorex Synthelabo, Maidenhead, Berkshire, UK, 1999.
- 77 Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002.



- 78 Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002.
- 79 Sweetman S (Ed): The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003.
- 80 Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002.
- 81 Sweetman S (Ed): The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, MICROMEDEX, Greenwood Village, Colorado, Edition expires 06/2003.
- 82 Product Information: Coartem(R) oral tablets, artemether lumefantrine oral tablets. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2013.
- 83 Product Information: Catapres(R) oral tablets, clonidine HCl oral tablets. Boehringer Ingelheim Pharmaceuticals, Inc. (per Manufacturer), Ridgefield, CT, 2012.
- 84 Product Information: Catapres-TTS(R) transdermal system, clonidine transdermal system. Boehringer Ingelheim Pharmaceuticals, Inc. (per Manufacturer), Ridgefield, CT, 2012.
- 85 Product Information: XALKORI(R) oral capsules, crizotinib oral capsules. Pfizer Labs (per FDA), New York, NY, 2013.
- 86 Product Information: SAVELLA(R) oral tablets, milnacipran hydrochloride oral tablets. Forest Pharmaceuticals, Inc, New York, NY, 2010.
- 87 Product Information: thioridazine HCl oral tablets, thioridazine HCl oral tablets. Sun Pharmaceutical Industries, Inc. (per DailyMed), Cranbury, NJ, 2014.
- 88 Product Information: EXJADE(R) oral suspension tablets, deferasirox oral suspension tablets. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2012.
- 89 Product Information: TAFINLAR oral capsules, dabrafenib oral capsules. GlaxoSmithKline (per FDA), Research Triangle Park, NC, 2014.
- 90 Product Information: PREZCOBIX(TM) oral tablets, darunavir cobicistat oral tablets. Janssen Pharmaceuticals, Inc. (per manufacturer), Titusville, NJ, 2015.
- 91 Product Information: PROPULSID(R) oral tablets, oral suspension, cisapride oral tablets, oral suspension. Janssen Pharmaceutica, Titusville, NJ, 2000.
- 92 Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. *Ann Fr Anesth Reanim* 1992; 11:629-635.
- 93 Montaz L, Varache N, Harry P, et al: Torsades de pointes during sultopride poisoning. *J Toxicol Clin Exp* 1992; 12:481-496.
- 94 Harry P: Acute poisoning by new psychotropic drugs. *Rev Prat* 1997; 47:731-735.
- 95 Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002.
- 96 Lande G, Drouin E, Gauthier C, et al: Arrhythmogenic effects of sultopride chlorhydrate: clinical and cellular electrophysiological correlation. *Ann Fr Anesth Reanim* 1992; 11:629-635.
- 97 Montaz L, Varache N, Harry P, et al: Torsades de pointes during sultopride poisoning. *J Toxicol Clin Exp* 1992; 12:481-496.
- 98 Harry P: Acute poisoning by new psychotropic drugs. *Rev Prat* 1997; 47:731-735.
- 99 Product Information: Geodon(R), ziprasidone. Pfizer Inc, NY, NY, 2002.
- 100 Product Information: SYLVANT(TM) intravenous injection, siltuximab intravenous injection. Janssen Biotech, Inc. (per FDA), Horsham, PA, 2014.



- 101 Product Information: FIRDAPSE oral tablets, amifampridine phosphate oral tablets. BioMarin Europe Limited (per EMA), London, United Kingdom, 2012.
- 102 Product Information: Eurartesim oral film-coated tablets, piperaquine tetraphosphate dihydroartemisinin oral film-coated tablets. Sigma-Tau Industrie Farmaceutiche Riunite S.p.A (per EMA), Rome, Italy, 2012.
- 103 Product Information: ZYDELIG(R) oral tablets, idelalisib oral tablets. Gilead Sciences, Inc. (per FDA), Foster City, CA, 2014.
- 104 Product Information: LYSODREN(R) oral tablets, mitotane oral tablets. Bristol-Myers Squibb Company (per manufacturer), Princeton, NJ, 2013.
- 105 Product Information: Vascor(R) bepridil HCl. McNeil Pharmaceutical, Spring House, PA, 2000.
- 106 Product Information: Seldane(R), terfenadine. Marion Merrell Dow, Kansas City, MO, 1996.
- 107 Product Information: ORAP(R) oral tablets, pimozide oral tablets. Gate Pharmaceuticals (per FDA), Sellersville, PA, 2011.
- 108 Product Information: ZAGAM(R) oral tablets, sparfloxacin oral tablets. Bertek Pharmaceuticals, Inc., Collegeville, PA, 2003.
- 109 Teva Canada Limited: Dear Healthcare Professional letter for domperidone maleate. Teva Canada Limited. Toronto, Canada. 2012. Available from URL: [http://www.hc-sc.gc.ca/dhp-mps/alt\\_formats/pdf/medeff/advisories-avis/prof/2012/domperidone\\_hpc-cps-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2012/domperidone_hpc-cps-eng.pdf). As accessed 2012-03-22.
- 110 Product Information: SERENTIL(R) oral tablets, injection, oral solution, mesoridazine besylate oral tablets, injection, oral solution. Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, 2001.
- 111 Australian Government Department of Health and Ageing Therapeutic Goods Administration: Amendments to the Prescribing Medicines in Pregnancy Booklet. Australian Government Department of Health and Ageing Therapeutic Goods Administration. Woden, Australia. 2006. Available from URL: <http://www.tga.gov.au/docs/html/mip/0606newmed.pdf>.
- 112 Product Information. Geodon™, ziprasidone, Pfizer Inc, New York, NY (PI issued reviewed 5/2001., 2/2001).
- 113 Product Information: GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, ziprasidone hydrochloride oral capsule, ziprasidone mesylate intramuscular powder for solution. Pfizer Roerig, New York, NY, 2005.
- 114 Prakash C, Kamel A, Cui D, et al: Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. *Br J Clin Pharmacol* 2000; 49(suppl 1):35S-42S.
- 115 Caccia S: Biotransformation of post-clozapine antipsychotics; pharmacological implications. *Clin Pharmacokinet* 2000; 38(5):393-414.
- 116 Wilner KD, Demattos SB, Anziano RJ, et al: Ziprasidone and the activity of cytochrome P450 2D6 in healthy extensive metabolizers. *Br J Clin Pharmacol* 2000a; 49(suppl 1):43S-47S.
- 117 Lincoln J, Stewart ME, & Preskorn SH: How sequential studies inform drug development: evaluating the effect of food intake on optimal bioavailability of ziprasidone. *J Psychiatr Pract* 2010; 16(2):103-114. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 118 Miceli JJ, Wilner KD, Hansen RA, et al: Single- and multiple-dose pharmacokinetics of ziprasidone under non- fasting conditions in healthy male volunteers. *Br J Clin Pharmacol* 2000; 49(suppl 1):5S-13S.
- 119 Miceli JJ, Hansen RA, Johnson AC, et al: Single and multiple dose pharmacokinetics of ziprasidone in healthy males (abstract). *Pharm Res* 1995; 12(suppl):392.
- 120 Ereshefsky L: Pharmacokinetics and drug interactions: update for new antipsychotics. *J Clin Psychiatry* 1996; 57(suppl):12-25.

- 121 None Listed: Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27(2):596-601. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 122 Marder SR, Essock SM, Miller AL, et al: Physical health monitoring of patients with schizophrenia. *Am J Psychiatry* 2004; 161(8):1334-1349. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 123 Ray WA, Chung CP, Murray KT, et al: Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360(3):225-235. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 124 Schneeweiss S & Avorn J: Antipsychotic agents and sudden cardiac death — How should we manage the risk?. *N Engl J Med* 2009; 360(3):294-296. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 125 Sacchetti E, Galluzzo A, Valsecchi P, et al: Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study. *Schizophr Res* 2009; 110(1-3):80-89. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 126 Anon: An expanding range of atypical antipsychotic agents to choose from (review). *Drugs Ther Perspect* 1996; 8:1-5.
- 127 Goff DC, Posever T, Herz L, et al: An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 1998; 18(4):296-304.
- 128 Brook S, Lucey JV, & Gunn KP: Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 2000; 61:933-941.
- 129 Hirsch SR, Kissling W, Bauml J, et al: A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. *J Clin Psychiatry* 2002; 63(6):516-523.
- 130 Rosenheck R & Lin H: Noninferiority of perphenazine vs. three second-generation antipsychotics in chronic schizophrenia. *J Nerv Ment Dis* 2014; 202(1):18-24. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 131 Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Eng J Med* 2005; 353:1209-1223.
- 132 Simpson GM, Glick ID, Weiden PJ, et al: Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2004; 161(10):1837-1847.
- 133 Breier A, Berg PH, Thakore JH, et al: Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. *Am J Psychiatry* 2005; 162:1879-1887.
- 134 Potkin SG, Ogasara M, Cucchiari J, et al: Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. *Schizophr Res* 2011; 132(2-3):101-107. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 135 Zhang Y & Dai G: Efficacy and metabolic influence of paliperidone ER, aripiprazole and ziprasidone to patients with first-episode schizophrenia through 52 weeks follow-up in China. *Hum Psychopharmacol* 2012; 27(6):605-614. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 136 Barry PJ, Gallagher P, Ryan C, et al: START (screening tool to alert doctors to the right treatment)--an evidence-based screening tool to detect prescribing omissions in elderly patients. *Age Ageing* 2007; 36(6):632-638. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 137 Gallagher P, Ryan C, Byrne S, et al: STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008; 46(2):72-83. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 138 Gallagher P & O'Mahony D: STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria (Supplementary Data). *Age Ageing* 2008; 37(6):1.
- 139 American Geriatrics Society 2012 Beers Criteria Update Expert Panel: American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2012; 60(4):616-631. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 140 Gallagher P & O'Mahony D: STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing* 2008; 37(6):673-679. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 141 January CT, Wann LS, Alpert JS, et al: 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; Epub:Epub. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 142 Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128(16):e240-e327. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 143 Weber MA, Schiffrin EL, White WB, et al: Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)* 2014; 16(1):14-26. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 144 Khanna D , Fitzgerald JD , Khanna PP , et al: 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)* 2012; 64(10):1431-1446. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 145 Hsieh C: Treatment of constipation in older adults. *Am Fam Physician* 2005; 72(11):2277-2284. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 146 Jneid H, Anderson JL, Wright RS, et al: 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2012; 126(7):875-910. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 147 Kearon C, Akl EA, Comerota AJ, et al: Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 suppl):e419S-e494S. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 148 Baldwin DS, Waldman S, & Allgulander C: Evidence-based pharmacological treatment of generalized anxiety disorder. *Int J Neuropsychopharmacol* 2011; 14(5):697-710. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 149 Davidson JR: First-line pharmacotherapy approaches for generalized anxiety disorder. *J Clin Psychiatry* 2009; 70 Suppl 2:25-31. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 150 Schutte-Rodin S, Broch L, Buysse D, et al: Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008; 4(5):487-504. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 151 Guerrant RL, Van Gilder T, Steiner TS, et al: Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis* 2001; 32(3):331-351. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 152 Talley NJ & Vakil N: Guidelines for the management of dyspepsia. *Am J Gastroenterol* 2005; 100(10):2324-2337. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 153 Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Bethesda, MD. 2013. Available from URL: [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report\\_2013Feb13.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013Feb13.pdf). As accessed 2014-08-12.
- 154 Bhatt DL, Scheiman J, Abraham NS, et al: ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008; 118(18):1894-1909. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 155 Zhang W, Moskowitz RW, Nuki G, et al: OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008; 16(2):137-162. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 156 American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum* 2002; 46(2):328-346. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 157 Lucas MG; Bedretdinova D; Bosch JLHR et al: Guidelines on urinary incontinence. European Association of Urology. Arnhem, Netherlands. 2014. Available from URL: [http://www.uroweb.org/gls/pdf/20%20Urinary%20Incontinence\\_LR.pdf](http://www.uroweb.org/gls/pdf/20%20Urinary%20Incontinence_LR.pdf). As accessed 2014-08-13.
- 158 World Health Organization (WHO): WHO's cancer pain ladder for adults. World Health Organization (WHO). Geneva, Switzerland. 2014. Available from URL: <http://www.who.int/cancer/palliative/painladder/en/>. As accessed 2014-08-12.
- 159 Newcomer JW: Metabolic syndrome and mental illness. *Am J Manag Care* 2007; 13(7 Suppl):S170-S177. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 160 Leucht S, Corves C, Arbtter D, et al: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2008; 373(9657):31-41. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 161 Hasnain M, Vieweg WV, Fredrickson SK, et al: Clinical monitoring and management of the metabolic syndrome in patients receiving atypical antipsychotic medications. *Prim Care Diabetes* 2008; Epub:1-. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 162 Newcomer JW: Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J Clin Psychiatry* 2007; 68(Suppl 1):20-27. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 163 Jin H, Meyer JM, & Jeste DV: Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res* 2004; 71(2-3):195-212. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 164 Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353(12):1209-1223. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 165 Stroup TS, Lieberman JA, McEvoy JP, et al: Results of phase 3 of the CATIE schizophrenia trial. *Schizophr Res* 2008; Epub:1. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 166 Amiel JM, Mangurian CV, Ganguli R, et al: Addressing cardiometabolic risk during treatment with antipsychotic medications. *Curr Opin Psychiatry* 2008; 21(6):613-618. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 167 Beers MH, Ouslander JG, Rollinger I, et al: Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med 1991; 151(9):1825-1832. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 168 Beers MH: Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997; 157(14):1531-1536. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 169 Fick DM, Cooper JW, Wade WE, et al: Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003; 163(22):2716-2724. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 170 Chutka DS, Takahashi PY, & Hoel RW: Inappropriate medications for elderly patients. Mayo Clin Proc 2004; 79(1):122-139. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 171 Jano E & Aparasu RR: Healthcare outcomes associated with beers' criteria: a systematic review. Ann Pharmacother 2007; 41(3):438-447. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 172 Jimenez-Jimenez FJ, Garcia-Ruiz PJ, & Molina JA: Drug-induced movement disorders. Drug Saf 1997; 16(3):180-204.
- 173 Batey SR: Schizophrenic disorders In: DiPiro JT, Talbert RL, Hayes PE, et al (Eds): Pharmacotherapy A Pathophysiologic Approach, Elsevier, New York, NY, 1989.
- 174 Shader RI & DiMascio A (Eds): Psychotropic Drug Side Effects, Williams and Wilkins Company, Maryland, 1977.
- 175 Ereshefsky L & Richards A: Psychoses In: Ereshefsky L & Richards A: Young LY & Koda-Kimble MA: Applied Therapeutics The Clinical Use of Drugs, 4th. Applied Therapeutics Inc, Vancouver, WA, 1988.
- 176 Gilman AG, Goodman LS, Rall TW, et al: Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 7th ed. Macmillan Publishing, New York, NY, 1985. Jeste DV & Wyatt RJ: Changing epidemiology of tardive dyskinesia: an overview. Am J Psychiatry 1981; 138:297-309.
- 177 Khakee A & Hess GF: Mellaril(R) in the treatment of chronically disturbed patients. Am J Psychiatry 1960; 116:1029.
- 178 Ananth J: Tardive dyskinesia: myths and realities. Psychosomatics 1980; 21:394-396.
- 179 Chien CP: Past history of drug and somatic treatments in tardive dyskinesia In: Fann WE, Smith RC, David JM, et al (Eds): Tardive Dyskinesia. Research and Treatment, SP Medical & Scientific Books, New York, NY, 1980, pp 315-324.
- 180 Crane GE: Persistent dyskinesia. Br J Psychiatry 1973; 122:395-405.
- 181 Lohr JB, Caligiuri MP, Edson R, et al: Treatment predictors of extrapyramidal side effects in patients with tardive dyskinesia: results from Veterans Affairs Cooperative Study 394. J Clin Psychopharmacol 2002; 22(2):196-200.
- 182 Grossman F: A review of anticonvulsants in treating agitated demented elderly patients. Pharmacotherapy 1998; 18(3):600-606.
- 183 Class CA, Schneider L, & Farlow MR: Optimal management of behavioural disorders associated with dementia. Drugs Aging 1997; 10(2):95-106.
- 184 Rabins PV, Blacker D, Rovner BW, et al: American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry 2007; 164(12 Suppl):5-56. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 185 U.S. Food and Drug Administration: Conventional Antipsychotics - Healthcare Professional Sheet text version. U.S. Food and Drug Administration. Rockville, MD. 2009. Available from URL: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm>. As accessed 2009-06-23.

- 186 Meeks TW & Jeste DV: Beyond the Black Box: What is The Role for Antipsychotics in Dementia?. *Curr Psychiatr* 2008; 7(6):50-65. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 187 Lanctot KL, Best TS, Mittmann N, et al: Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. *J Clin Psychiatry* 1998; 59(10):550-561. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 188 Borson S & Raskind MA : Clinical features and pharmacologic treatment of behavioral symptoms of Alzheimer's disease. *Neurology* 1997; 48(5 Suppl 6):S17-S24. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 189 Mintzer JE, Hoernig KS, & Mirski DF: Treatment of agitation in patients with dementia. *Clin Geriatr Med* 1998; 14(1):147-175.
- 190 Verma SD, Davidoff DA, & Kambhampati KK: Management of the agitated elderly patient in the nursing home: the role of the atypical antipsychotics. *J Clin Psychiatry* 1998; 59(suppl 19):50-55.
- 191 Tariot PN: Treatment of agitation in dementia. *J Clin Psychiatry* 1999; 60(suppl):11-20.
- 192 Herrmann N: Valproic acid treatment of agitation in dementia. *Can J Psychiatry* 1998; 43:69-72.
- 193 Rita Moretti, MD, Universita degli Studi di Trieste
- 194 Pollock BG & Mulsant BH: Behavioral disturbances of dementia. *J Geriatr Psychiatry Neurol* 1998; 11:206-212.
- 195 Nyth AL, Gottfries CG, Lyby K, et al: A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. *Acta Psychiatr Scand* 1992; 86:138-145.
- 196 Nyth AL & Gottfries CG: The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicentre study. *Br J Psychiatry* 1990; 157:894-901.
- 197 Serra-Mestres J, Shapleske J, & Tym E: Treatment of palilalia with trazodone (letter). *Am J Psychiatry* 1996; 153:580-581.
- 198 Raskind MA, Cyrus PA, Ruzicka BB, et al: The effects of Metrifonate on the cognitive, behavioral, and functional performance of Alzheimer's Disease in patients. *J Clin Psychiatry* 1999; 60:318-325.
- 199 Shelton PS & Brooks VG: Estrogen for dementia-related aggression in elderly men. *Ann Pharmacother* 1999; 33:808-812.
- 200 Reich SD: Antineoplastic agents as potential carcinogens: Are nurses and pharmacists at risk?. *Cancer Nurs* 1981; 4:500-502.
- 201 Knowles RS & Virden JE: Handling of injectable antineoplastic agents. *BMJ* 1980; 281:589-591.
- 202 Harrison BR: Developing guidelines for working with antineoplastic drugs. *Am J Hosp Pharm* 1981; 38:1686-1693.
- 203 Centers for Disease Control and Prevention (CDC): NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2012. Centers for Disease Control and Prevention (CDC). Atlanta, GA. 2012. Available from URL: <http://www.cdc.gov/niosh/docs/2012-150/pdfs/2012-150.pdf>. As accessed 2013-05-14.
- 204 Anon: ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990; 47:1033-1049.
- 205 Product Information: Geodon™, ziprasidone, Pfizer Inc, New York, NY. PI issued 2/2001, 2001.
- 206 Green K & Parish RC: Stability of ziprasidone mesylate in an extemporaneously compounded oral solution. *J Pediatr Pharmacol Ther* 2010; 15(2):138-141. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

DRUGDEX is a registered trademark of Thomson Healthcare Inc. All Micromedex Systems are Copyright © Thomson Micromedex. All rights reserved.



The information contained in the Micromedex products is intended as an educational aid only. The information contained in these products is being provided to legal professionals and is not intended for use by legal professionals for patient treatment purposes. All Treatments or procedures are intended to serve as an information resource for physicians or other competent healthcare professionals performing the consultation or evaluation of patients and must be interpreted in view of all attendant circumstances, indications and contraindications. The use of the Micromedex products is at your sole risk. These products are provided "AS IS" and "AS AVAILABLE" for use, without warranties of any kind, either express or implied. Micromedex makes no representation or warranty as to the accuracy, reliability, timeliness, usefulness or completeness of any of the information contained in the products. Additionally, Micromedex makes no representation or warranties as to the opinions or other service or data you may access, download or use as a result of use of the Micromedex products. **ALL IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE OR USE ARE HEREBY EXCLUDED. MICROMEDEX DOES NOT ASSUME ANY RESPONSIBILITY OR RISK FOR YOUR USE OF THE MICROMEDEX PRODUCTS.**

---

End of Document

© 2017 Thomson Reuters. No claim to original U.S. Government Works.