DRUGDEX® Evaluations

DEXMETHYLPHENIDATE

0.0 Overview

1) Class
- **a)** This drug is a member of the following class(es):
  Amphetamine Related
  CNS Stimulant

2) Dosing Information
- **a)** Dexmethylphenidate Hydrochloride
  - **1)** Adult
    - **a)** Attention deficit hyperactivity disorder
      1) extended-release: methylphenidate-naive patients, initial 10 mg ORALLY daily in the morning; adjust dose weekly in 10 mg increments; MAX 20 mg/day
      2) extended-release: patients currently using methylphenidate, one-half the total daily dose of racemic methylphenidate; patients currently using dexmethylphenidate immediate-release may be switched to the same daily dose of dexmethylphenidate extended-release; MAX 20 mg/day
  - **2)** Pediatric
    - **a)** safety and efficacy not established in patients under 6 years of age
      - **1)** Attention deficit hyperactivity disorder
        a) immediate-release (ages 6 years and older): methylphenidate-naive patients, initial 2.5 mg ORALLY twice daily; adjust dose weekly in 2.5 to 5 mg increments; MAX 20 mg/day (10 mg twice a day)
        b) immediate-release (ages 6 years and older): patients currently using methylphenidate, one-half the dose of racemic methylphenidate; MAX 20 mg/day (10 mg twice a day)
        c) extended-release (ages 6 years and older): methylphenidate-naive patients, initial 5 mg ORALLY in the morning; adjust dose weekly in 5 mg increments; MAX 20 mg/day(Prod Info FOCALIN XR(R) extended-release oral capsules, 2008)
        d) extended-release (ages 6 years and older): patients currently using methylphenidate, one-half the total daily dose of racemic methylphenidate; patients currently using immediate release dexmethylphenidate may be switched to the same daily dose of dexmethylphenidate extended release (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008)

3) Contraindications
- **a)** Dexmethylphenidate Hydrochloride
  1) agitation, severe; anxiety; or tension; may aggravate symptoms (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  2) glaucoma (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  3) hypersensitivity to methylphenidate or other components of the product (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  4) MAOI use within 14 days; hypertensive crisis may result (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  5) motor tics (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
  6) Tourette's syndrome, family history or diagnosis of (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

4) Serious Adverse Effects
- **a)** Dexmethylphenidate Hydrochloride
  1) Mania
  2) Psychotic disorder
  3) Seizure

5) Clinical Applications
- **a)** Dexmethylphenidate Hydrochloride
  - **1)** FDA Approved Indications
    - **a)** Attention deficit hyperactivity disorder

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

Dexmethylphenidate
Dexmethylphenidate HCl
Dexmethylphenidate Hydrochloride

C) Physicochemical Properties

1) Molecular Weight

a) 269.77(Prod Info Focalin™, 2001a)

2) Solubility

a) Systemic: Freely soluble in water and in methanol; soluble in alcohol; slightly soluble in chloroform and in acetone (Prod Info Focalin™, 2001a)

1.2 Storage and Stability

A) Oral route

1) The US manufacturer recommends storage of dexmethylphenidate tablets and capsules at 25 degrees C (77 degrees F), with excursions permitted to 15 to 30 degrees C (59 to 86 degrees F). Tablets should be protected from moisture (Prod Info FOCALIN(TM) XR, 2005; Prod Info Focalin(TM), 2001d).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.3.1 Normal Dosage

1.3.1.A Dexmethylphenidate Hydrochloride

1.3.1.A.1 Oral route

1.3.1.A.1.a Attention deficit hyperactivity disorder

1) Extended-Release

a) The recommended starting dose for patients not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 10 milligrams (mg)/day in the morning. The dose may be adjusted weekly in 10 mg increments to a maximum of 20 mg/day for adult patients. The patient should be observed for a sufficient duration at a given dose to ensure that a maximal benefit has been achieved before a dose increase is considered (Prod Info FOCALIN(TM) XR, 2005).

b) For patients currently using methylphenidate, the recommended starting dose is half the total daily dose of racemic methylphenidate. Patients using immediate-release dexmethylphenidate may be switched to the same daily dose of extended-release dexmethylphenidate. Maximum recommended dose is 20 milligrams/day (Prod Info FOCALIN (TM) XR, 2005).

c) The treatment duration is unclear, however, it is generally agreed that pharmacological treatment of ADHD may be needed for extended periods. The patient should be periodically reevaluated with periods off medication to assess patient's functioning without pharmacotherapy (Prod Info FOCALIN(TM) XR, 2005).

d) If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced or, if necessary, the drug should be discontinued (Prod Info FOCALIN(TM) XR, 2005).

e) If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued (Prod Info FOCALIN(TM) XR, 2005).

1.3.2 Dosage in Renal Failure

A) Dexmethylphenidate Hydrochloride

1) Pharmacokinetic data for dexmethylphenidate in renal impairment are unavailable. However, data for racemic methylphenidate indicate that only small amounts are excreted unchanged in the urine (about 1%)

(USPDI, 2001; Prod Info Focalin(TM), 2001); thus, dose adjustments of dexmethylphenidate do not appear to be necessary in this population.

1.3.3 Dosage in Hepatic Insufficiency

A) Dexmethylphenidate Hydrochloride

1) Similar to methylphenidate, dexmethylphenidate undergoes hepatic metabolism (USPDI, 2001); (Prod Info Focalin(TM), 2001). Dose adjustment should be considered in patients with moderate or greater hepatic dysfunction. Specific guidelines for dexmethylphenidate or the racemic compound are unavailable.

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

1.4.1 Normal Dosage

1.4.1.A Dexmethylphenidate Hydrochloride

1.4.1.A.1 Oral route

1.4.1.A.1.a Attention deficit hyperactivity disorder

1) Immediate-Release

a) The efficacy of dexmethylphenidate has been demonstrated only in patients 6 to 17 years of age. The drug should be given twice daily, at least 4 hours apart; it can be given with or without food (Prod Info Focalin(TM), 2001).

b) In patients not currently receiving racemic methylphenidate, or for those who are on stimulants other than methylphenidate, the manufacturer recommends an initial dose of 2.5 milligrams (mg) twice daily, with dose adjustments in 2.5- to 5-mg increments to a maximum of 10 mg twice daily; dose adjustments may be undertaken at approximately weekly intervals (Prod Info Focalin(TM), 2001). An extended-release methylphenidate formulation (duration, 8 hours) may be preferable, as administration of doses during school can be eliminated; generic formulations are available.

c) For patients who are currently receiving racemic methylphenidate, the initial dose recommended by manufacturer is half the dose of methylphenidate, with a maximum daily dose of 20 mg (10 mg twice daily) (Prod Info Focalin(TM), 2001). However, available data suggest no clinical advantage in switching to the d-enantiomer.

d) The longest duration of effective treatment in clinical studies with dexmethylphenidate has been 6 weeks (Prod Info Focalin(TM), 2001). However, prolonged use may be indicated. Racemic methylphenidate has maintained improvement for up to 2 years.

2) Extended-Release

a) The recommended starting dose for patients not currently taking dexmethylphenidate or racemic methylphenidate, or for patients who are on stimulants other than methylphenidate, is 5 milligrams (mg)/day in the morning. The dose may be adjusted weekly in 5 mg increments to a maximum of 20 mg/day for pediatric patients. The patient should be observed for a sufficient duration at a given dose to ensure that a maximal benefit has been achieved before a dose increase is considered (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

b) For patients currently using methylphenidate, the recommended starting dose is half the total daily dose of racemic methylphenidate. Patients using immediate-release dexmethylphenidate may be switched to the same daily dose of extended-release dexmethylphenidate. Maximum recommended dose is 20 milligrams/day (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

c) The treatment duration is unclear, however, it is generally agreed that pharmacological treatment of ADHD may be needed for extended periods. The patient should be periodically reevaluated with periods off medication to assess patient's functioning without pharmacotherapy (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

d) If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced or, if necessary, the drug should be discontinued (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

e) If improvement is not observed after appropriate dosage adjustment over a 1-month period, the drug should be discontinued (Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

1.4.2 Dosage in Renal Failure

A) Dexmethylphenidate Hydrochloride

1) Pharmacokinetic data for dexmethylphenidate in renal impairment are unavailable. However, data for racemic methylphenidate indicate that only small amounts are excreted unchanged in the urine (about 1%) (USPDI, 2001; Prod Info Focalin(TM), 2001). Thus, dose adjustments of dexmethylphenidate do not appear necessary in this population.

1.4.3 Dosage in Hepatic Insufficiency

A) Dexmethylphenidate Hydrochloride

1) Similar to methylphenidate, dexmethylphenidate undergoes hepatic metabolism (USPDI, 2001; Prod Info Focalin(TM), 2001). Dose adjustment should be considered in patients with moderate or greater hepatic dysfunction. Specific guidelines for dexmethylphenidate or the racemic compound are unavailable.

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Dexmethylphenidate Hydrochloride

a) Initial Response

1) Attention-deficit hyperactivity disorder, oral extended-release tablets: 1 hour (Prod Info FOCALIN (TM) XR, 2005)

a) Value represents time to a significant treatment effect in pediatric patients after a single dose of 20 milligrams (Prod Info FOCALIN(TM) XR, 2005).

2) Attention-deficit hyperactivity disorder, oral immediate-release tablets: within 4 weeks (sustained improvement) (Anon, 2001).

a) Value represents time to significant symptom improvement during continuous twice-daily administration.

B) Duration

1) Dexmethylphenidate Hydrochloride

a) Multiple Dose

1) Attention deficit hyperactivity disorder, ORAL: up to 6.5 hours (acute effects) (Anon, 1999).

2) Attention deficit hyperactivity disorder, Oral: 12 hours in pediatric patients 6 to12 years old (Prod Info FOCALIN(TM) XR, 2005)

a) Represents interpretation of data from one unpublished study, which suggested a longer duration of action of dexmethylphenidate than racemic methylphenidate in ADHD (Anon, 1999). In this study, control of symptoms with dexmethylphenidate was seen at all time points, but there was failure of methylphenidate to control symptoms at the last measurements (5.5 to 6.5 hours postdose). However, specific time points evaluated in the study, the duration of action of methylphenidate, and statistical comparisons at these time points are not available; thus, the difference in duration between these agents in this study is unknown. In other studies, racemic methylphenidate has shown a duration of 4 to 6 hours, and the difference in durations between these agents must be small, and may not be clinically relevant. Extended-release methylphenidate is often used in ADHD, which has a longer duration than that reported for dexmethylphenidate (8 hours).

2.2 Drug Concentration Levels

A) Dexmethylphenidate Hydrochloride

1) Therapeutic Drug Concentration

a) Not established; plasma-level monitoring is not used clinically.

2) Time to Peak Concentration

a) Oral, immediate-release tablet: 1 to 1.5 hours (Prod Info Focalin™, 2001a).

1) This value is similar to that reported for racemic methylphenidate (about 2 hours).

2) Following oral doses of 2.5, 5, and 10 mg in children (as a capsule formulation), peak plasma levels and AUCs of dexmethylphenidate were proportional to the dose; plasma levels were similar to those observed after oral racemic methylphenidate 5, 10, and 20 mg (Prod Info Focalin™, 2001a).

3) No significant accumulation of dexmethylphenidate has been observed with repeated twice-daily doses compared to single doses in ADHD patients (Prod Info Focalin™, 2001a).

b) Oral, extended-release tablet: 1.5 hours (first peak) and 6.5 hours (second peak) (Prod Info FOCALIN (TM) XR, 2005).

1) The mean time to the first peak (tmax1) (1.5 hours) is similar to the tmax for the immediate-release formulation. The time to the second peak (tmax2) (6.5 hours) is slightly longer for the extended-release formulation given once-daily compared to the immediate-release formulation given in 2 doses 4 hours apart (Prod Info FOCALIN(TM) XR, 2005).

3) Area Under the Curve

a) The AUC after administration of dexmethylphenidate hydrochloride extended-release tablets given once daily is equivalent to the same total dose of dexmethylphenidate hydrochloride immediate-release tablets given in 2 doses 4 hours apart; variability in AUC is similar between the extended- and immediate-release tablets with approximately a three-fold range in each (Prod Info FOCALIN(TM) XR, 2005).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Dexmethylphenidate Hydrochloride

1) Bioavailability

a) Oral, various: mean absolute bioavailability 22 to 25% (Prod Info FOCALIN(TM) XR, 2005).

1) Dexmethylphenidate is well absorbed after oral administration with approximately 90% recovered in the urine. However, due to first-pass metabolism, the mean absolute bioavailability when administered in various formulations was 22 to 25% (Prod Info FOCALIN(TM) XR, 2005).

2) Effects of Food

a) immediate-release tablet, delayed absorption (Prod Info Focalin™, 2001a).

1) In an unpublished study, administration of dexmethylphenidate with food had no significant effect on extent of absorption compared to the fasting state (based on peak plasma levels and AUC values); however, time to peak plasma levels was prolonged when given with food (mean, 2.9 versus 1.5 hours) (Prod Info Focalin™, 2001a). Dexmethylphenidate can be given with or without food.

b) extended-release tablet, unknown (Prod Info FOCALIN(TM) XR, 2005)

1) No food effect study was performed with the extended-release formulation; administration times relative to meals and meal composition may need to be individually titrated (Prod Info FOCALIN (TM) XR, 2005).

2) Effect of food: oral, racemic methylphenidate extended release tablets, following high fat breakfast, delayed absorption and second peak concentration is approximately 25% lower. Can be administered with or without food (Prod Info FOCALIN(TM) XR, 2005).

2.3.2 Distribution

A) Distribution Sites

1) Dexmethylphenidate Hydrochloride

a) Protein Binding

1) A specific value for dexmethylphenidate is unavailable. However, protein binding of racemic methylphenidate is minimal (12 to 15%) .(Prod Info FOCALIN(TM) XR, 2005)

B) Distribution Kinetics

1) Dexmethylphenidate Hydrochloride

a) Volume of Distribution

1) 2.65 L/kg (+/- 1.1 L/kg) (Prod Info FOCALIN(TM) XR, 2005).

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) Dexmethylphenidate Hydrochloride

a) LIVER, extensive (Prod Info Focalin™, 2001a).

1) The primary metabolic pathway is deesterification to the inactive metabolite d-ritalinic acid (d-alpha-phenyl piperidine acetic acid) (Prod Info Focalin™, 2001a).

2) Inhibition of cytochrome P450 isozymes was not observed with dexmethylphenidate in vitro (Prod Info Focalin™, 2001a).

3) Bioconversion to l-dexmethylphenidate is negligible (Prod Info Focalin™, 2001a) and of no

clinical consequence.

B) Metabolites

1) Dexmethylphenidate Hydrochloride

a) d-Ritalinic acid (inactive) (Prod Info Focalin™, 2001a).

2.3.4 Excretion

A) Kidney

1) Dexmethylphenidate Hydrochloride

a) Renal Clearance (rate)

1) Intravenous dexmethylphenidate was eliminated with a mean clearance of 0.56 +/- 0.18 liter/minute (Prod Info FOCALIN(TM) XR, 2005)

b) Renal Excretion (%)

1) minimal unchanged (Prod Info Focalin™, 2001a).

c) Specific renal excretion data for dexmethylphenidate are unavailable. However, approximately 90% of an oral dose of racemic methylphenidate appears in the urine, mainly as ritalinic acid (about 80%); 0.5% appears as unchanged methylphenidate following an intravenous dose (Prod Info FOCALIN(TM) XR, 2005; Prod Info Focalin™, 2001a).

2.3.5 Elimination Half-life

A) Parent Compound

1) Dexmethylphenidate Hydrochloride

a) ELIMINATION HALF-LIFE

1) approximately 3 hours (Prod Info FOCALIN(TM) XR, 2005; Prod Info Focalin™, 2001a).

a) The mean terminal elimination half-life of dexmethylphenidate was just over 3 hours in healthy adults and typically varied between 2 and 4.5 hours; children displayed shorter half-lives with means of 2 to 3 hours (Prod Info FOCALIN(TM) XR, 2005).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Dexmethylphenidate Hydrochloride

a) Oral (Capsule, Extended Release; Tablet)

1) Dexmethylphenidate hydrochloride should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006).

3.1 Contraindications

A) Dexmethylphenidate Hydrochloride

1) agitation, severe; anxiety; or tension; may aggravate symptoms (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

2) glaucoma (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

3) hypersensitivity to methylphenidate or other components of the product (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

4) MAOI use within 14 days; hypertensive crisis may result (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

5) motor tics (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

6) Tourette's syndrome, family history or diagnosis of (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

3.2 Precautions

A) Dexmethylphenidate Hydrochloride

1) cardiac abnormalities, structural; sudden death has been reported in association with CNS stimulant use(Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
2) conditions which may be compromised by increases in blood pressure or heart rate, such as pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
3) depression, severe; do not use to treat (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
4) drug dependence or alcoholism, history of; potential for abuse (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
5) EEG abnormalities, especially history of; may lower convulsive threshold (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
6) fatigue, normal; do not use to treat (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
7) psychosis; may exacerbate behavior disturbance and thought disorder (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)
8) seizures, especially history of; may lower convulsive threshold (Prod Info FOCALIN(TM) XR extended-release oral capsules, 2006)

3.3 Adverse Reactions

Cardiovascular Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hematologic Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Other

3.3.1 Cardiovascular Effects

3.3.1.A Dexmethylphenidate Hydrochloride

3.3.1.A.1 Cardiovascular finding

a) Modest increases in heart rate (up to 5 beats per minute) and systolic/diastolic blood pressure (up to 3 mmHg) have been reported during dexmethylphenidate therapy in children/adolescents with ADHD (unpublished clinical studies) (Prod Info Focalin(TM), 2001). TACHYCARDIA has rarely necessitated withdrawal of treatment (Prod Info Focalin(TM), 2001).

3.3.3 Endocrine/Metabolic Effects

3.3.3.A Dexmethylphenidate Hydrochloride

3.3.3.A.1 Metabolic finding

a) Whether prolonged use of methylphenidate (or dexmethylphenidate) can significantly limit height and body weight remains controversial. Monitoring of weight and height is indicated in preadolescent children. Early adolescent growth does not appear to be affected by methylphenidate.

3.3.4 Gastrointestinal Effects

3.3.4.A Dexmethylphenidate Hydrochloride

Abdominal pain

Loss of appetite

Nausea

3.3.4.A.1 Abdominal pain

a) Incidence: 15% (Prod Info FOCALIN(R) oral tablets, 2007)

b) In unpublished clinical-trial data for dexmethylphenidate in children/adolescents with ADHD, abdominal pain was reported at least once during treatment in 15% of patients. Incidences of these effects were at least 50% lower in placebo recipients (Prod Info FOCALIN(R) oral tablets, 2007). There is no demonstrated evidence of a lower frequency of GI effects in patients treated with dexmethylphenidate compared to racemic methylphenidate.

3.3.4.A.2 Loss of appetite

a) Incidence: 6% (Prod Info FOCALIN(R) oral tablets, 2007)

b) In unpublished clinical-trial data for dexmethylphenidate in children/adolescents with ADHD, anorexia was reported at least once during treatment in 6% of patients. Incidences of these effects were at least 50% lower in placebo recipients (Prod Info FOCALIN(R) oral tablets, 2007). There is no demonstrated evidence of a lower frequency of GI effects in patients treated with dexmethylphenidate compared to racemic methylphenidate.

3.3.4.A.3 Nausea

a) Incidence: 9% (Prod Info FOCALIN(R) oral tablets, 2007)

b) In unpublished clinical-trial data for dexmethylphenidate in children/adolescents with ADHD, nausea was reported at least once during treatment in 9% of patients. Incidences of these effects were at least 50% lower in placebo recipients (Prod Info FOCALIN(R) oral tablets, 2007). There is no demonstrated evidence of a lower frequency of GI effects in patients treated with dexmethylphenidate compared to racemic methylphenidate.

3.3.5 Hematologic Effects

3.3.5.A Dexmethylphenidate Hydrochloride

3.3.5.A.1 Hematology finding

a) Thrombocytopenia and anemia have occurred infrequently during racemic methylphenidate therapy (USPDI, 2001); (Prod Info Focalin(TM), 2001). The manufacturer of dexmethylphenidate has not disclosed the frequency of these effects in clinical trials, although this data is available from extensive premarketing safety evaluations (Prod Info Focalin(TM), 2001).

3.3.9 Neurologic Effects

3.3.9.A Dexmethylphenidate Hydrochloride

Insomnia

Spasmodic movement, Vocal or motor tics

3.3.9.A.1 Insomnia

a) Nervousness and insomnia have occurred relatively frequently with use of racemic methylphenidate in children and adolescents, and may be more common in children (USPDI, 2001); (Prod Info Focalin (TM), 2001).

b) In clinical studies specifically with dexmethylphenidate in ADHD, the manufacturer indicates that motor or vocal tics and insomnia have rarely (1%) necessitated therapy discontinuation (Prod Info Focalin(TM), 2001). However, the manufacturer has chosen not to disclose the frequency of other CNS effects in clinical trials, although this data was available from extensive premarketing safety evaluations (Prod Info Focalin(TM), 2001).

c) Although dexmethylphenidate is claimed to potentially produced fewer adverse CNS effects (eg, insomnia) than racemic methylphenidate (Anon, 2001a), this has not been demonstrated.

3.3.9.A.2 Spasmodic movement, Vocal or motor tics

a) In clinical studies specifically with dexmethylphenidate in ADHD, the manufacturer indicates that motor or vocal tics and insomnia have rarely (1%) necessitated therapy discontinuation (Prod Info Focalin(TM), 2001). However, the manufacturer has chosen not to disclose the frequency of other CNS effects in clinical trials, although this data was available from extensive premarketing safety evaluations (Prod Info Focalin(TM), 2001).

3.3.10 Ophthalmic Effects

3.3.10.A Dexmethylphenidate Hydrochloride

3.3.10.A.1 Eye / vision finding

a) Similar to racemic methylphenidate, dexmethylphenidate is capable of infrequently causing blurring of vision and other visual disturbances (USPDI, 2001); (Prod Info Focalin(TM), 2001). However, specific incidence data for these effects were not disclosed by the manufacturer of dexmethylphenidate.

3.3.12 Psychiatric Effects

3.3.12.A Dexmethylphenidate Hydrochloride

Mania

Psychotic disorder

Seizure

3.3.12.A.1 Mania

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mosholder et al, 2009).

3.3.12.A.2 Psychotic disorder

a) In a review of 49 randomized, controlled pediatric ADHD clinical trials involving pscyhostimulant medications (atomoxetine hydrochloride, methylphenidate hydrochloride, modafinil and dextromethylphenidate hydrochloride), the rate of psychosis/mania events in pediatric subjects receiving active drug was 1.48 (95% CI, 0.74 to 2.65) per 100 person-years, with no comparable adverse events recorded in the placebo group. A request from the US Food and Drug Administration to manufacturers of marketed ADHD drugs for submission of postmarketing case reports of psychosis or mania events between 2000 and 2005, yielded a total of 865 reports (pediatrics and adults) in which signs and/or symptoms of psychoses or mania were reported. The majority of reports involved pediatric subjects, with almost half of the reports in children 10 years-old or younger, and approximately 90% of cases involving no prior history of similar psychiatric conditions. Visual and/or tactile sensations of insects, snakes, or worms were commonly reported. Positive rechallenge was reported for each of the psychostimulant medications (methylphenidate hydrochloride, atomoxetine hydrochloride, and mixed salts of a single entity amphetamine product) included in the analysis; and in many cases a strong temporal association was identified. The onset of psychiatric symptoms ranged from days to weeks, but in some cases it was months or years from the start of ADHD treatment and symptom onset (Mosholder et al, 2009).

b) Seizures and psychosis have occurred rarely with racemic methylphenidate (USPDI, 2001)

3.3.12.A.3 Seizure

a) Seizures and psychosis have occurred rarely with racemic methylphenidate (USPDI, 2001)

3.3.16 Other

3.3.16.A Dexmethylphenidate Hydrochloride

Drug dependence

Fever

3.3.16.A.1 Drug dependence

a) Similar to methylphenidate, both psychological and physical dependence can occur during high-dose and/or prolonged use of dexmethylphenidate. The manufacturer (Prod Info Focalin(TM), 2001) suggests only the risk of psychological dependence.

b) Slow tapering of the dose is required following long-term therapy or use of high doses to minimize withdrawal symptoms, which can include unusual tiredness, severe depression, and unusual behavior (USPDI, 2001).

3.3.16.A.2 Fever

a) In unpublished clinical-trial data for dexmethylphenidate in children/adolescents with ADHD, fever was reported at least once during treatment in 5% of patients; fever occurred in 1% of placebo recipients (Prod Info Focalin(TM), 2001).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info FOCALIN XR, 2008) (All Trimesters)

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Although a causal relationship between dexmethylphenidate and teratogenic effects have not been found, the safe use of dexmethylphenidate during pregnancy has yet to be confirmed. Until additional data are available, dexmethylphenidate should be used in pregnant women only if the benefit to the pregnant woman outweighs the potential risk to the fetus (Prod Info FOCALIN XR, 2008).

4) Literature Reports

a) No human studies of pregnancy outcomes after exposure to dexmethylphenidate have been published, and there are no reports of outcomes after inadvertent exposure during pregnancy. Adequate studies to establish safe use of dexmethylphenidate during pregnancy have not been conducted (Prod Info FOCALIN XR, 2008). One source describes a series of women (n=11) who used racemic methylphenidate (dose unspecified) during the first 4 months of pregnancy; no birth defects or other abnormalities were reported in any of the infants and all 11 were considered normal (Heinonen et al, 1977). A later report discussed the outcomes of another 38 women who used racemic methylphenidate during pregnancy (DeBooy et al, 1993). Although infants in these reports were more likely to be premature, growth retarded, and to show signs of neonatal withdrawal, no increase in congenital abnormalities was identified; however, this number is so small that no pattern or estimate of risk can be determined at this time. No teratogenicity was observed in rats and rabbits treated with dexmethylphenidate in doses up to 20 and 100 milligrams/kilogram (mg/kg) daily, respectively, during the period of organogenesis; however, delayed fetal skeletal ossification was seen at the highest dose in rats. However, doses of 200 mg/kg/day of racemic methylphenidate have produced teratogenic effects in rabbits throughout organogenesis (Prod Info FOCALIN XR, 2008).

B) Breastfeeding

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

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

2) Clinical Management

a) It is not known whether dexmethylphenidate is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown (Prod Info FOCALIN XR, 2008).

3) Literature Reports

a) Four published case reports indicate that maternal doses of racemic methylphenidate of 35 to 80 mg/day during breastfeeding resulted in milk concentrations that ranged from undetectable to 15.4 ng/mL (calculated infant daily dose approximately 0.4 to 2.9 ug/kg/day or approximately 0.2% to 0.7% of the adjusted maternal weight dose) for an exclusively breastfed infant (Prod Info FOCALIN XR, 2008).

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Amitriptyline

Amoxapine

Brofaromine

Clomipramine

Clorgyline

Desipramine

Dicumarol

Dothiepin

Doxepin

Furazolidone

Imipramine

Iproniazid

Isocarboxazid

Lazabemide

Linezolid

Lofepramine

Moclobemide

Nialamide

Nortriptyline

Opipramol

Pargyline

Phenelzine

Phenobarbital

Phenytoin

Primidone

Procarbazine

Protriptyline

Rasagiline

Selegiline

Toloxatone

Tranylcypromine

Trimipramine

Warfarin

3.5.1.A Amitriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.B Amoxapine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other

sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.C Brofaromine

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.D Clomipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline

results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.E Clorgyline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.F Desipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as

high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.G Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: Dexmethylphenidate may inhibit the metabolism of coumarin anticoagulants, such as dicumarol, potentially resulting in an increased risk of bleeding. Dicumarol dosage may need to be reduced during concurrent dexmethylphenidate therapy. When initiating or discontinuing dexmethylphenidate therapy, it may be necessary to adjust the dicumarol dose and monitor coagulation times (Prod Info FOCALIN(R) XR extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider reducing the dicumarol dose during concomitant dexmethylphenidate therapy due to an increased risk of bleeding. Adjust the dose as needed and monitor coagulation times when initiating or discontinuing dexmethylphenidate treatment (Prod Info FOCALIN(R) XR extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of dicumarol metabolism

3.5.1.H Dothiepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled

steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.I Doxepin

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.J Furazolidone

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.K Imipramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation

2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.

7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission

8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.L Iproniazid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.

7) Probable Mechanism: unknown

3.5.1.M Isocarboxazid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.N Lazabemide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.O Linezolid

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.P Lofepramine

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the

methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.Q Moclobemide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.R Nialamide

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.S Nortriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism

of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.T Opipramol

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.U Pargyline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by

symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.V Phenelzine
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.W Phenobarbital
1) Interaction Effect: increase in phenobarbital plasma concentrations
2) Summary: Pharmacologic studies have demonstrated that dexmethylphenidate may inhibit the metabolism of anticonvulsants, such as phenobarbital. Dose adjustments of phenobarbital may be necessary (Prod Info Focalin(TM), 2001c).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Downward dose adjustments of phenobarbital may be required when given concomitantly with dexmethylphenidate.
7) Probable Mechanism: inhibition of phenobarbital metabolism by dexmethylphenidate

3.5.1.X Phenytoin
1) Interaction Effect: increase in phenytoin plasma concentrations
2) Summary: Pharmacologic studies have demonstrated that dexmethylphenidate may inhibit the metabolism of anticonvulsants, such as phenytoin. Dose adjustments of phenytoin may be necessary (Prod Info Focalin(TM), 2001).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Downward dose adjustments of phenytoin may be required when given concomitantly with dexmethylphenidate.
7) Probable Mechanism: inhibition of phenytoin metabolism by dexmethylphenidate

3.5.1.Y Primidone
1) Interaction Effect: increase in primidone plasma concentrations
2) Summary: Pharmacologic studies have demonstrated that dexmethylphenidate may inhibit the metabolism of anticonvulsants, such as primidone. Dose adjustments of primidone may be necessary (Prod Info Focalin(TM), 2001a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Downward dose adjustments of primidone may be required when given concomitantly with dexmethylphenidate.
7) Probable Mechanism: inhibition of primidone metabolism by dexmethylphenidate

3.5.1.Z Procarbazine
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid

5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AA Protriptyline

1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports

a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).

b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).

c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).

d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).

e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AB Rasagiline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AC Selegiline

1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)

2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AD Toloxatone
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AE Tranylcypromine
1) Interaction Effect: hypertensive crisis (headache, palpitation, and neck stiffness)
2) Summary: Monoamine oxidase inhibitors should not be administered with sympathomimetic drugs such as dexmethylphenidate. Coadministration may result in hypertensive crisis, which is characterized by symptoms such as headache, palpitation, neck stiffness, nausea, and vomiting. Hypertensive crisis associated with monoamine oxidase inhibitors has been fatal (Prod Info Focalin(TM), 2001b).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent use of monoamine oxidase inhibitors and dexmethylphenidate is contraindicated. If dexmethylphenidate is to be initiated, the monoamine oxidase inhibitor must be discontinued for a minimum of 14 days.
7) Probable Mechanism: unknown

3.5.1.AF Trimipramine
1) Interaction Effect: hypertension, other cardiac effects, and CNS stimulation
2) Summary: Concomitant tricyclic antidepressant (TCA) and amphetamine administration has been reported to result in enhanced amphetamine effects from the release of norepinephrine (Beaumont, 1973; Raisfeld, 1972). A similar reaction might also occur with all drugs that have amphetamine-like effects. Acute elevations in blood pressure have been noted (Flemenbaum, 1971a). Some amphetamine-like drugs may inhibit the metabolism of TCAs, although most combinations have not been studied. When amphetamine analogs are being used to treat obesity, it should be noted that TCAs frequently lead to moderate weight gain (Russ & Ackerman, 1988). False positive urine tests for amphetamines have been reported during therapy with some TCAs (Merigian & Browning, 1993). Caution is advised when concurrent administration of amphetamine-like agents and TCAs is warranted. The patient should be closely monitored for increased cardiovascular effects (hypertension and dysrhythmias).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of amphetamines and tricyclic antidepressants or other sympathomimetic agents could lead to hypertension, increased cardiovascular effects, or CNS stimulation (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006; Flemenbaum, 1972). Use caution if such therapy is warranted. Monitor the patient closely for hypertension and dysrhythmias.
7) Probable Mechanism: synergistic effects on noradrenergic neurotransmission
8) Literature Reports
a) Amphetamines may increase the activity of tricyclic antidepressants (TCA) or sympathomimetic agents. Additionally, coadministration of d-amphetamine with TCAs such as desipramine or protriptyline results in sustained increases in d-amphetamine concentration in the brain (Prod Info VYVANSE(TM) oral capsules, 2007; Prod Info DEXEDRINE(R) sustained-release oral capsules, oral tablets, 2006; Prod Info ADDERALL(R) oral tablets, 2006).
b) Human pharmacologic studies have demonstrated that methylphenidate may inhibit the metabolism

of some tricyclic antidepressants, such as imipramine, clomipramine, or desipramine (Prod Info DAYTRANA(TM) transdermal system, 2006).
c) Concomitant administration of tricyclic antidepressants and methylphenidate can result in increases in blood pressure such that the hypotensive effects induced by TCAs may lead to blood pressures as high as 170/120 mmHg within one day of combined therapy. Discontinuation of the methylphenidate usually results in the blood pressure returning to normotensive levels; reinstitution of the methylphenidate resulted in further blood pressure elevation (Flemenbaum, 1971; Flemenbaum, 1972).
d) Fifteen patients with DSM-III major depression, who failed to respond to treatment with desipramine given for at least four weeks, were given fenfluramine 40 mg to 120 mg daily for two weeks but did not result in any transient or sustained clinical improvement. However, fenfluramine more than doubled steady-state plasma levels of desipramine (Price et al, 1990).
e) There have been claims based on uncontrolled studies that a better antidepressant response may occur with combined therapy (Garrettson et al, 1969). However, a systemic review of stimulants in the treatment of depression concluded that although uncontrolled studies were generally positive, the ten placebo-controlled studies of stimulant drugs in primary depression, with one exception, indicated little advantage of drug over placebo and did not appear to be as effective as the conventional antidepressants in primary depression (Satel & Nelson, 1989).

3.5.1.AG Warfarin
1) Interaction Effect: an increased risk of bleeding
2) Summary: Dexmethylphenidate may inhibit the metabolism of coumarin anticoagulants, such as warfarin, potentially resulting in an increased risk of bleeding. Warfarin dosage may need to be reduced during concurrent dexmethylphenidate therapy. When initiating or discontinuing dexmethylphenidate therapy, it may be necessary to adjust the warfarin dose and monitor coagulation times (Prod Info FOCALIN(R) XR extended-release oral capsules, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider reducing the warfarin dose during concomitant dexmethylphenidate therapy due to an increased risk of bleeding. Adjust the dose as needed and monitor coagulation times when initiating or discontinuing dexmethylphenidate treatment (Prod Info FOCALIN(R) XR extended-release oral capsules, 2007).
7) Probable Mechanism: inhibition of warfarin metabolism

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) Dexmethylphenidate Hydrochloride
1) Therapeutic
a) Physical Findings
1) Improvement in mental and behavioral symptoms of attention deficit hyperactivity disorder (ADHD), including inappropriate inattention, impulsivity, hyperactivity, and cognitive performance.
a) For the inattentive type of ADHD, these include lack of sustained attention, no attention to details, inability to follow through on tasks, poor listener, avoidance of tasks requiring sustained mental effort, and easily distracted.
b) For the hyperactive-impulsive type, these include fidgeting or squirming, excessive talking, leaving seat, inappropriate climbing or running, intrusiveness, and difficulty with quiet activities.
c) If symptoms do not improve within one month (including appropriate dose adjustments), the drug should be discontinued (Prod Info FOCALIN(R) oral tablets, 2007a).
2) Periodic reassessment of the need for continued dexmethylphenidate treatment (by temporarily withdrawing therapy and monitoring for recurrence of behavioral symptoms and their severity; slow dose-tapering may be indicated to prevent withdrawal symptoms) (Prod Info FOCALIN(R) oral tablets,

2007a).

2) Toxic

a) Laboratory Parameters

1) Monitor complete blood count with differential and platelets periodically during extended therapy (Prod Info FOCALIN(R) oral tablets, 2007a).

b) Physical Findings

1) The American Academy of Pediatrics (AAP) does not recommend the routine use of electrocardiograms (ECGS) or routine subspecialty cardiology evaluations (which were previously recommended by the American Heart Association (AHA) scientific statement to detect cardiac conditions that might place the child at risk for sudden cardiac death) before initiating stimulant therapy to treat attention-deficit/hyperactivity disorder ADHD in most children. The APA cited specific reasons for changing the recommendation including: lack of evidence establishing a relationship between stimulant drugs used to treat ADHD and sudden cardiac death (SCD), the frequency of sudden unexpected deaths among patients taking stimulant drugs is not higher than that in the general population of children, and lack of cost-effective analysis to support ECG screening or special evaluation by pediatric cardiologist (Perrin et al, 2008).

2) Based on the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) consensus statements, the following cardiac monitoring recommendations have been established to assist clinicians in the evaluation of children treated with stimulant drugs, including dexmethylphenidate, for ADHD (Perrin et al, 2008; Vetter et al, 2008):

- Conduct a thorough examination prior to initiating dexmethylphenidate therapy for a diagnosis of ADHD. Special attention should be given to symptoms indicative of a cardiac condition, including palpitations, near syncope, or syncope.
- Obtain a complete family and patient history for conditions associated with SCD, and determine current use of any other prescription or over-the-counter medications.
- Conduct a complete physical evaluation of the patient for hypertension, cardiac murmurs, physical findings associated with Marfan syndrome, and signs of irregular cardiac rhythms.
- Perform further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist .
- Continue to assess the patient for cardiac symptoms and any changes in family history at follow up visits.
- Blood pressure and heart rate should be evaluated at baseline, during routine follow-up within 1 to 3 months, and at follow up visits every 6 to 12 months. Increases in blood pressure and heart rate have been reported with stimulant use.

3) Assess growth determinations (body weight and height) periodically (Prod Info FOCALIN(R) oral tablets, 2007a).

4) Determine the amount and frequency of medication during prolonged treatment (for detection of potential tolerance/dependence).

4.2 Patient Instructions

A) Dexmethylphenidate (By mouth)

Dexmethylphenidate

Treats attention deficit hyperactivity disorder (ADHD).

When This Medicine Should Not Be Used:
You should not use this medicine if you or your child have had an allergic reaction to dexmethylphenidate. You should not use this medicine if you have glaucoma, or if you are anxious, tense, or agitated most of the time. You should not use this medicine if you have muscle tics or Tourette's syndrome, a condition that causes you to have muscle twitches or to makes sounds you are not able to control. Do not use this medicine if you have taken an MAO inhibitor (Eldepryl®, Marplan®, Nardil®, Parnate®) within the past 14 days. This medicine should not be given to a child under 6 years of age unless your doctor tells you otherwise.

How to Use This Medicine:
Tablet, Long Acting Capsule

Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it more often than your doctor tells you to.
This medicine should come with a Medication Guide. Read and follow these instructions carefully. Ask your doctor or pharmacist if you have any questions. Ask your pharmacist for the Medication Guide if you do not have one. Your doctor might ask you to sign some forms to show that you understand this information.
You may take this medicine with or without food.
This medicine is usually given once daily. Because dexmethylphenidate can cause a loss of appetite, it is best to take the medicine after eating or just before your morning meal, unless your doctor tells you otherwise.
Swallow the extended-release capsule whole. Do not crush, break, or chew it.
If you cannot swallow the extended-release capsule, you may open it and pour the medicine into a small amount of soft food such as pudding, yogurt, or applesauce. Stir this mixture well and swallow it without

chewing.
Always take this medicine with a full glass of liquid (water, milk, or juice).

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

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are also using blood pressure medicines, blood thinners (such as Coumadin®, warfarin), clonidine (Catapres®, Clorpres®, Combipres®), or medicines to treat seizures (such as Dilantin®, Luminal®, Mysoline®). Tell your doctor if you use medicines for depression (such as amitriptyline, imipramine, trazodone, Celexa®, Effexor®, Luvox®, Norpramin®, Paxil®, Prozac®, Serzone®, Vivactil®, or Zoloft®).
Tell your doctor if you use cold or allergy medicines, or antacids or stomach acid reducers (such as Axid®, Prilosec®, Tagamet®, or Zantac®).

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant, planning to become pregnant, or breastfeeding, or if you or your child have kidney problems, liver problems, heart disease, heart rhythm problems, or high blood pressure. Your doctor should know if you or your child have epilepsy, a history of seizures, depression or mental illness, or drug or alcohol problems. Also tell your doctor if you or anyone in your family has tried to commit suicide.
This medicine may be habit-forming. If you feel that the medicine is not working as well, do not use more than your prescribed dose. Call your doctor for instructions.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.
This medicine may cause slow growth. If your child is using this medicine, the doctor will need to keep track of your child's height and weight to make sure that your child is growing properly.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Blurred vision, trouble seeing.
Chest pain or shortness of breath.
Fast, pounding, or irregular heartbeat.
Lightheadedness, dizziness, or fainting.
Mood or mental changes, confusion, or unusual behavior.
Seizures.
Tremors or shaking.
Uncontrollable muscle movements or twitching.
Unusual bleeding, bruising, or weakness.
Vomiting, agitation, confusion, sweating, fever.

If you notice these less serious side effects, talk with your doctor:
Dry mouth or nose.
Feeling restless or nervous.
Headache.
Nausea, loss of appetite, or stomach pain.
Trouble sleeping.

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

4.3 Place In Therapy

A) SUMMARY

1) Clinical data for dexmethylphenidate at present do not support its use over methylphenidate in ADHD. It is not

recommended for the hospital formulary.

B) ATTENTION-DEFICIT HYPERACTIVITY DISORDER

1) Pharmacologic therapy is indicated as an adjunct to other measures (eg, counseling) in patients with attention-deficit hyperactivity disorder (ADHD). The mainstays of drug therapy are the stimulants methylphenidate, dextroamphetamine, and pemoline; these agents are similarly effective, although pemoline is used less frequently initially due to its slow onset. In patients not responding well to stimulants, bupropion, desipramine, clonidine, or MAO inhibitors may find usefulness, although adverse effects may prove problematic.

2) Dexmethylphenidate, the d-enantiomer of methylphenidate, is indicated for the treatment of ADHD in patients aged 6 years and older. Two placebo-controlled studies in patients meeting DSM-IV criteria for ADHD demonstrated dexmethylphenidate's effectiveness in the treatment of ADHD in patients 6 years of age and older.

3) A slightly longer duration of action has been reported for dexmethylphenidate compared to regular-release methylphenidate, although this appears to be small and is probably of no clinical relevance; both agents are recommended twice daily at similar intervals. Extended-release methylphenidate is used commonly in children to eliminate the need for methylphenidate dosing at school, and has a duration exceeding that of methylphenidate and dexmethylphenidate by at least two hours. Both regular-release and extended-release methylphenidate products are available generically at a lower cost than dexmethylphenidate.

4.4 Mechanism of Action / Pharmacology

A) Dexmethylphenidate Hydrochloride

1) MECHANISM OF ACTION

a) Dexmethylphenidate is the d-enantiomer (also known as d-threo-enantiomer) of methylphenidate (Ritalin (R)), the latter of which exists as the racemate (d,l-enantiomers in a 1:1 ratio) (Anon, 1999; Prod Info Focalin™, 2001a). Dexmethylphenidate accounts for most or all clinical effects of racemic methylphenidate (Anon, 2001; Prod Info Focalin™, 2001a).

b) Dexmethylphenidate is claimed to have efficacy similar to or greater than methylphenidate in attention-deficit hyperactivity disorder (ADHD), with a lower propensity for adverse effects; as it is one of the quantitatively equal enantiomers, it can be given in half the dose of the racemic compound, and this is also claimed to be an advantage (Anon, 2001a; Anon, 2001; Anon, 2000).

c) The mechanism of racemic methylphenidate in ADHD has not been fully elucidated. Both methylphenidate and dexmethylphenidate appear to inhibit reuptake of dopamine and norepinephrine into presynaptic neurons (Prod Info Focalin™, 2001a), increasing availability of these neurotransmitters in the extraneuronal space.

4.5 Therapeutic Uses

4.5.A Dexmethylphenidate Hydrochloride

4.5.A.1 Attention deficit hyperactivity disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (extended-release only); Pediatric, yes (age 6 yr and older)
Efficacy: Adult, Evidence favors efficacy; Pediatric, Effective
Recommendation: Adult, Class IIa; Pediatric, Class IIa
Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Extended-release dexmethylphenidate was superior to placebo for the treatment of attention deficit/hyperactivity disorder (ADHD) in children (Silva et al, 2008; Brams et al, 2008; Prod Info FOCALIN XR(R) extended-release oral capsules, 2008).

Fixed-dose dexmethylphenidate extended-release (ER) was superior to placebo for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults in a 5-week, randomized double-blind, placebo-controlled trial (n=218) (Spencer et al, 2007).

Dexmethylphenidate extended-release (ER) was superior to placebo for the treatment of pediatric ADHD in a 7-week , randomized, double-blind, placebo-controlled study (n=97) (Greenhill et al, 2006).

Results of two unpublished studies suggest the efficacy of oral immediate-release dexmethylphenidate in children and adolescents with ADHD (Prod Info Focalin(TM), 2001)

The efficacy of dexmethylphenidate is similar to that of racemic methylphenidate

c) Adult:

1) Evaluated Data

a) There are no studies evaluating the efficacy of immediate-release dexmethylphenidate in adults with attention-deficit hyperactivity disorder (ADHD).

2) Clinical Study Summaries

a) In an unpublished study, dexmethylphenidate extended-release was found to be more effective than placebo for the treatment of adults (ages 18 to 60) who met DSM-IV criteria for attention-deficit hyperactivity disorder (ADHD). In a randomized, double-blind, parallel-group study, patients (n=221) were randomized to either a fixed dose (20, 30, or 40 milligrams (mg)/day) of dexmethylphenidate extended-release or placebo once daily for 5 weeks. Treatment was initiated

at 10 mg/day and was titrated in increments of 10 mg weekly to the assigned fixed dose. Efficacy was measured by comparing the mean change in signs and symptoms of ADHD from baseline to endpoint using an intent-to-treat analysis of the investigator-administered DSM-IV ADHD Disorder Rating Scale. All 3 doses were found to be superior to placebo, with no apparent advantage with increasing dose (Prod Info FOCALIN(TM) XR, 2005).

3) Extended-Release

a) Fixed-dose dexmethylphenidate extended-release (ER) was superior to placebo for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults in a 5-week, multicenter, randomized double-blind, parallel-group, placebo-controlled trial (n=218). Adult patients aged 18 to 60 years (yr) (mean, 38.7 years) who met the following criteria were included: a DSM-IV diagnosis of ADHD of any subtype with childhood onset of symptoms, a total score of at least 24 at screening and at baseline on the DSM-IV ADHD rating scale (RS), and a Global Assessment of Functioning (GAF) score of 60 or less. All patients were required to discontinue all psychotropic medications within 1 to 4 weeks prior to the screening visit. Patients were equally randomized to dexmethylphenidate ER 20 milligrams (mg) (n=58), 30 mg (n=55) or 40 mg (n=55) daily or to placebo (n=53) for 5 weeks. The primary outcome was the change from baseline to final visit in the DSM-IV ADHD-RS total score. Analysis was performed on the modified intent-to-treat population, defined as all randomized patients who received at least 1 dose of study medication and had at least 1 pre- and post randomization assessment for change in DSM-IV ADHD-RS total score. The analysis revealed that all doses of dexmethylphenidate ER were superior to placebo for improvement of DSM-IV ADHD-RS total score. The mean change from baseline to final visit in DSM-IV ADHD-RS total score was 13.7 (from 36.8 to 23.1; p=0.006) for dexmethylphenidate ER 20 mg, 13.4 (from 36.9 to 23.5; p=0.012) for 30 mg, 16.9 (36.9 to 20; p=0.001) for 40 mg, and 7.9 (37.5 to 29.6) for placebo. The most common adverse effects were headache (31.5% vs 18.9%), decreased appetite (18.2% vs 11.3%), insomnia (16.4% vs 11.3%), dry mouth (15.8% vs 3.8%; p less than 0.05), and jitteriness (12.1% vs 1.9%; p less than 0.05) in the consolidated dexmethylphenidate ER groups compared with the placebo group. The authors note limitations of short study duration and insufficient power for direct comparison between doses (Spencer et al, 2007).

d) Pediatric:

1) Evaluated Data

a) No studies with dexmethylphenidate immediate-release have been published. In studies sponsored by the manufacturer, dexmethylphenidate 5 to 20 milligrams (mg) daily was reported statistically superior to placebo in children/adolescents (6 to 17 years) with attention-deficit hyperactivity disorder (ADHD), based on various behavior scales (Anon, 1999; Anon, 1999a; Anon, 2001; Prod Info Focalin(TM), 2001). One of these studies employed short-term (2-week) drug withdrawal following open-label treatment, where failure rates were lower in children continuing dexmethylphenidate (about 20%) compared to those given placebo (63%)(Prod Info Focalin(TM), 2001).

b) However, data released for these studies are incomplete, and the actual number of trials conducted is unclear. Pertinent clinical details not provided include demographic data (importantly, baseline severity of ADHD in each group), doses associated with response (or mean or maximum effective doses), specific statistical-analysis data (or tests used), and details of evaluation methods.

c) Dexmethylphenidate has been compared with methylphenidate in at least one of these studies, although comparative efficacy results were not reported. Press releases from the manufacturer regarding these comparisons are unclear and confusing (Anon, 1999; Anon, 2001; Anon, 1999b). Overall, the two drugs appear similarly effective, with a similar adverse-effect profile. Although dexmethylphenidate can be given in half the dose of methylphenidate, this is not a clinical advantage.

2) Immediate Release

a) One unpublished, placebo-controlled study from the package insert involving 132 patients with ADHD (6 to 17 years) reported significantly greater improvement of symptom scores from baseline on the Swanson, Noland, and Pelham (SNAP)-ADHD rating scale with dexmethylphenidate 5 to 20 mg daily (two divided doses, 3.5 to 5.5 hours apart) than with placebo (mean change, -0.7 versus -0.2). This study assessed improvements over 4 weeks. Patients included had all subtypes of ADHD (combined type, inattentive type, hyperactive-impulsive type) (Prod Info Focalin(TM), 2001). This trial directly compared dexmethylphenidate to racemic methylphenidate (10 to 40 mg daily), although no results for methylphenidate were provided.

3) Extended-Release

a) A randomized, double-blind, placebo-controlled, crossover study revealed extended-release dexmethylphenidate was superior to placebo for the treatment of attention deficit/hyperactivity disorder (ADHD) in children (n=68). Children aged 6 to 12 years (mean 9.5 years; 66.2% male) who met Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for any type of ADHD, who were clinically and behaviorally stable and without medication changes for at least 2 weeks were randomized to receive dexmethylphenidate extended release (d-MPH-ER) 20 milligram (mg) capsules daily for 7 days or to placebo, with treatment crossover, beginning on day 8 for an additional 7 days. Efficacy was assessed as change in the Swanson, Kotkin, Agler, M-Flynn and Pelham rating scale (SKAMP)-combined score from predose to time points 0.5, 1, 3, 4,

5, 7, 9, 10, 11 and 12 hours (hr), and math test performance in a laboratory classroom setting, with the SKAMP scale defined as 13 items of measurement that provides individual and combined scores on the core ADHD symptoms of attention and deportment. The intent-to-treat analysis revealed that d-MPH-ER was significantly superior to placebo in improvement of the SKAMP-combined score from predose to 0.5 hr postdose (adjusted mean change of score, -2.242 versus 3.493; p=0.001) and at all other time points (p less than or equal to 0.001). D-MPH-ER was associated with 8.6% improvement in SKAMP-combined score compared to 66.7% worsening with placebo. Change from predose in individual SKAMP attention scores (p less than or equal to 0.001) and deportment scores (p=0.003 or less) were significantly improved at all time points. Math test performance scores were significantly improved at all postdose time points in attempted test questions (p less than 0.001) and correctly-answered test questions (p less than 0.001). The most common adverse effect was upper respiratory tract infection, not otherwise specified (d-MPH-ER, 4.4% vs placebo, 7.4%). One serious adverse effect of 3+ proteinuria was reported during the d-MPH-ER phase, which was not attributed to study medication and resolved without sequelae (Silva et al, 2008).

b) A randomized, double-blind, placebo-controlled, crossover study revealed that extended-release dexmethylphenidate was superior to placebo for the treatment of attention deficit/hyperactivity disorder (ADHD) in children (n=86); however, the study was underpowered. Children (mean age 9.5 years (yr), range 6 to 12 yr, 61.6% male) diagnosed with any type of ADHD using the DSM-IV criteria, who were clinically and behaviorally stable and without medication changes for at least 2 weeks were randomized to receive dexmethylphenidate extended release (d-MPH-ER) 20 milligram (mg) capsules daily for 7 days or to placebo, with treatment crossover, beginning on day 8 for an additional 7 days. The primary outcome was change in the Swanson, Kotkin, Agler, M-Flynn and Pelham rating scale (SKAMP)-combined score from predose to 0.5 hours (hr) postdose, during an 8-hr laboratory classroom setting, with the SKAMP scale defined as 13 items of measurement that provides individual and combined scores on the core ADHD symptoms of attention and deportment. The intent-to-treat analysis revealed d-MPH-ER was significantly superior to placebo in improvement of the SKAMP-combined score from predose to 0.5 hr postdose with an adjusted mean change score of -0.969 vs 3.336 (p less than 0.001), and at all other postdose time points (1, 2, 4, 6, 8 hr) (p less than 0.001). Change in individual SKAMP attention and deportment scores were significantly improved at all time points (p less than or equal to 0.001). In addition, change from baseline in the Conners' ADHD/DSM-IV scale for parents (CADS-P), which assesses the childs' behavior with and without treatment, was significantly improved with d-MPH-ER compared with placebo (adjusted least-square mean -16.38 vs -4.62; difference, -11.76; 95% confidence interval (CI), -15.36 to -8.16; p less than 0.001). Dexmethylphenidate was associated with higher incidence of headache (3.5% vs 2.3%) compared with placebo (Brams et al, 2008).

c) Dexmethylphenidate extended-release (ER) was superior to placebo for the treatment of pediatric ADHD in a 7-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, two-phase study (n=97). Pediatric patients aged 6 to 17 years (yr) who met DSM-IV criteria for ADHD of any type were eligible. All patients must be functioning at an age-appropriate academic level and the use of psychotropic medications or initiation of psychotropic medications within the past 3 months was not allowed. Any current treatment for ADHD was discontinued at least 7 days before baseline during the pre-randomization phase (up to 2 weeks). At the end of the pre-randomization phase, patients were randomized to receive either dexmethylphenidate ER 5 mg (n=52) or placebo (n=45) daily. In the double-blind treatment-phase, patients proceeded with dose titration to 5 or 10 mg/day for week 2; 5, 10 or 15 mg/day for week 3; then 5, 10, 15 or 20 mg/day for week 4. For treatment weeks 5 to 7, doses were titrated and maintained at optimal doses of 5, 10, 15, 20 or 30 mg/day. The mean final dexmethylphenidate ER dose was 24 +/- 7.1 mg/day. The primary outcome was the change from baseline to final visit in the Conners ADHD/DSM-IV Scale-Teacher version (CADS-T) total subscale score. Analysis was performed on the modified intent-to-treat population, defined as patients who received at least 1 dose of study medication and had at least 1 postbaseline CADS-T measurement. The analysis revealed that dexmethylphenidate ER was significantly superior to placebo in improvement from baseline to final visit in the CADS-T total score. The adjusted mean change in CADS-T total score from baseline to final visit was 16.3 in the dexmethylphenidate ER group compared with 5.7 in the placebo group (p less than 0.001). Similarly, dexmethylphenidate ER was superior to placebo in secondary outcome measures of mean change from baseline in the CADS-T Inattentive subscale score (8.1 vs 3.3; p=0.001) and in the Hyperactive-Impulsive subscale score (8.2 vs 2.5; p less than or equal to 0.001), respectively. The most common adverse effects attributed to study medication were decreased appetite (28.3% vs 6.4%), headache (24.5% vs 10.63%), nausea (11.3 vs 6.4%) and insomnia (7.5% vs 6.4%) in the dexmethylphenidate ER and placebo groups, respectively. No serious adverse events were reported. The authors note study limitations of short study duration and small sample size (Greenhill et al, 2006).

4.6 Comparative Efficacy / Evaluation With Other Therapies

4.6.A Methylphenidate

4.6.A.1 Attention deficit hyperactivity disorder

a) No comparisons with methylphenidate have been published, and data released by the manufacturer have not emphasized comparative efficacy, although this data is available. In a completed 4- week, placebo-controlled study described in the package insert (Prod Info Focalin(TM), 2001d), dexmethylphenidate 5 to 20 milligrams (mg) daily was compared to methylphenidate 10 to 40 mg daily (each in two divided doses) in patients with ADHD (n=132, 6 to 17 years of age). Patients included had all subtypes of ADHD (combined type, inattentive type, hyperactive-impulsive type). Dexmethylphenidate was reported to provide significantly greater improvement of symptom scores from baseline on the Swanson, Noland, and Pelham (SNAP)-ADHD rating scale compared to placebo (mean change, -0.7 versus -0.2). Although methylphenidate was the comparator, no results for methylphenidate were provided.

b) In manufacturer releases, apparently referring to the same package insert trial described above, the efficacy and safety of dexmethylphenidate were reported similar to methylphenidate (Anon, 2001)(Anon, 2001a). Earlier releases also did not indicate a significant difference in efficacy between the two drugs (Anon, 1999; Anon, 1999a), although they were carefully prepared to avoid this conclusion.

c) One manufacturer release suggested a longer duration of action of dexmethylphenidate in ADHD; in this study, control of symptoms with dexmethylphenidate was reportedly seen at all time points, but there was failure of methylphenidate to control symptoms at the last measurements (5.5 to 6.5 hours postdose) (Anon, 1999). However, the duration of action of methylphenidate was not given, precluding assessment of the duration of methylphenidate relative to dexmethylphenidate. The duration of dexmethylphenidate in this trial was similar to that of methylphenidate in other studies (4 to 6 hours), suggesting this difference is small. No study has provided comparative improvements in symptom scores from baseline, or statistical comparisons at all time points.

d) Available studies have not indicated a more favorable adverse- effect profile for dexmethylphenidate compared to methylphenidate (Anon, 1999a); (Anon, 2001).

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DRUGDEX® Evaluations

ZIPRASIDONE

0.0 Overview

1) Class

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

2) Dosing Information

a) Ziprasidone Hydrochloride

1) Adult

a) Bipolar I disorder, acute manic or mixed episodes

1) day 1, 40 mg twice daily with food; day 2, 60 or 80 mg twice daily; then adjust to 40 to 80 mg twice daily (Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Schizophrenia

1) initial, 20 mg ORALLY twice a day with food; may increase dosage every 2 days up to 80 mg twice a day (Prod Info GEODON(R) oral capsules, IM injection, 2007)

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007)

[redacted] capsules, IM injection, 2007)

b) Ziprasidone Mesylate

1) Adult

a) Agitation, acute - Schizophrenia

1) 10 mg IM every 2 hr (MAX dose 40 mg/day) OR 20 mg IM every 4 hr (MAX dose 40 mg/day); oral ziprasidone should replace IM administration as soon as possible; IM administration for more than 3 consecutive days has not been studied (Prod Info GEODON(R) oral capsules, IM injection, 2007)

2) Pediatric

a) safety and effectiveness in pediatric patients have not been established (Prod Info GEODON(R) oral capsules, IM injection, 2007)

3) Contraindications

a) Ziprasidone Hydrochloride

1) cardiac arrhythmias, history (Prod Info GEODON(R) oral capsules, IM injection, 2008)

2) 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3) heart failure, uncompensated (Prod Info GEODON(R) oral capsules, IM injection, 2008)

4) hypersensitivity to ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2008)

5) myocardial infarction, acute and recent (Prod Info GEODON(R) oral capsules, IM injection, 2008)

6) QT prolongation history including congenital long QT syndrome (Prod Info GEODON(R) oral capsules, IM injection, 2008)

b) Ziprasidone Mesylate

1) cardiac arrhythmias, history (Prod Info GEODON(R) oral capsules, IM injection, 2007)

2) concomitant use 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3) heart failure, uncompensated (Prod Info GEODON(R) oral capsules, IM injection, 2008)

4) hypersensitivity to ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2008)

5) myocardial infarction, acute and recent (Prod Info GEODON(R) oral capsules, IM injection, 2008)

6) QT prolongation, history including congenital long QT syndrome (Prod Info GEODON(R) oral capsules, IM injection, 2008)

4) Serious Adverse Effects

a) Ziprasidone Hydrochloride

1) Death

2) Diabetes mellitus

3) Hyperglycemia

4) Neuroleptic malignant syndrome

5) Priapism

6) Prolonged QT interval
7) Seizure
8) Syncope
9) Tardive dyskinesia
10) Torsades de pointes

b) Ziprasidone Mesylate
1) Death
2) Diabetes mellitus
3) Hyperglycemia
4) Priapism
5) Prolonged QT interval
6) Seizure
7) Syncope
8) Tardive dyskinesia
9) Torsades de pointes

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

b) Ziprasidone Mesylate
1) FDA Approved Indications
a) Agitation, acute - Schizophrenia

1.0 Dosing Information

Drug Properties

Storage and Stability

Adult Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms
Ziprasidone
Ziprasidone HCl
Ziprasidone Hydrochloride
Ziprasidone Mesylate

C) Physicochemical Properties
1) Molecular Weight
a) 467.42(Prod Info Geodon™, 2001)

1.2 Storage and Stability

A) Ziprasidone Hydrochloride
1) Preparation
a) Oral route
1) Oral ziprasidone hydrochloride capsules should be taken with food (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).
2) Administration
a) Ziprasidone mesylate injection should only be administered by intramuscular injection (IM) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

1.3.1 Normal Dosage

Ziprasidone Hydrochloride

Ziprasidone Mesylate

1.3.1.A Ziprasidone Hydrochloride

1.3.1.A.1 Oral route

Bipolar I disorder, acute manic or mixed episodes

Schizophrenia

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

1) For bipolar mania, the recommended initial dose is 40 milligrams twice daily with food. On the second day of treatment, the dose should be increased to 60 or 80 milligrams twice daily and thereafter adjusted according to tolerance and efficacy within the range of 40 to 80 milligrams twice daily. There are no recommendations for maintenance treatment (Prod Info GEODON(R) oral capsules, IM injection, 2007).

1.3.1.A.1.b Schizophrenia

1) For schizophrenia the initial daily dose is 20 milligrams (mg) twice daily with food. In some patients daily dosage may be adjusted up to 80 mg twice daily. Adjustments, if indicated, should occur at intervals of not less than 2 days. Efficacy in short-term clinical trials occurred with dosages between 20 to 100 mg twice daily. Initial dosages above 80 mg twice daily are not recommended and the safety of dosages above 100 mg twice daily have not been evaluated. To ensure the lowest effective dose, patients should be observed for improvement for several weeks before upward dosage adjustment (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).
2) Ziprasidone 10 milligrams (mg) intramuscularly (IM) produced a rapid reduction in symptoms of acute agitation and was significantly more effective (p less than 0.01) compared to a 2 mg IM dose up to 4 hours after the first injection (Lesem et al, 2001).

1.3.2 Dosage in Renal Failure
A) Ziprasidone Hydrochloride
1) No dosage adjustment should be necessary for mild-to-moderate renal impairment. No clinically significant effect on oral ziprasidone pharmacokinetics was found in these patients (Prod Info GEODON(R) oral capsules, IM injection, 2007; Aweeka et al, 2000).
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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007; Everson et al, 2000).

1.3.4 Dosage in Geriatric Patients
A) Ziprasidone Hydrochloride
1) No dosage adjustment is thought to be necessary for elderly patients; no clinically significant difference in ziprasidone pharmacokinetics was found between healthy young and elderly volunteers (Prod Info GEODON(R) oral capsules, IM injection, 2007; Wilner et al, 2000).
B) Ziprasidone Mesylate
1) Intramuscular ziprasidone mesylate has not been systematically evaluated in elderly patients. Dosage adjustment is not necessary in the elderly for oral ziprasidone hydrochloride; no clinically significant difference in pharmacokinetics was found between healthy young and elderly volunteers (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration
A) Onset
1) Peak Response
a) SCHIZOPHRENIA, ORAL: 4 weeks (Harrigan et al, 1996).

2.2 Drug Concentration Levels
A) Time to Peak Concentration
1) ORAL: 4 to 5 hours (Miceli et al, 2000a; Ereshefsky, 1996; Miceli et al, 1995).
a) Fed, 4.5 hours; fasted, 3.6 hours (Hamelin et al, 1998).
2) INTRAMUSCULAR: 60 minutes (Prod Info Geodon(R), 2002ae).
B) Area Under the Curve
1) 627.2 ng x hr/mL fed; 371.0 ng x hr/mL fasted (Hamelin et al, 1998).
a) Oral, fed, multiple-dose: 109.8 to 1027.9 ng x hr/mL (10 to 120 mg/day) (Miceli et al, 2000a).
b) Steady-state pharmacokinetics of ziprasidone did not differ between genders (Caccia, 2000).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption

A) Bioavailability
- **1)** ORAL: 60% (Ereshefsky, 1996; Miceli et al, 1995).
- **2)** INTRAMUSCULAR: 100% (Prod Info Geodon(R), 2002ae).

B) Effects of Food
- **1)** increased bioavailability (Ereshefsky, 1996; Miceli et al, 1995).
  - **a)** Dosing concurrent with high-fat meals increases systemic exposure to the drug, including area under the time-concentration curve, maximum concentration, and time to maximum concentration, while decreasing half-life (Caccia, 2000; Hamelin et al, 1998).

2.3.2 Distribution

A) Distribution Sites
- **1)** Protein Binding
  - **a)** Greater than 99% (Prod Info Geodon(R), 2002ae; Aweeka et al, 2000a; Everson et al, 2000a; Ereshefsky, 1996).

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

2.3.3 Metabolism

A) Metabolism Sites and Kinetics
- **1)** LIVER, (Prod Info Geodon(R), 2002ae; Ereshefsky, 1996).
  - **a)** CYP3A4 is the predominant isoenzyme involved in ZIPRASIDONE metabolism (Prakash et al, 2000; Caccia, 2000).
  - **b)** ZIPRASIDONE does not cause clinically significant inhibition of CYP2D6 (Wilner et al, 2000a; Prakash et al, 2000).

B) Metabolites
- **1)** Metabolites inactive at 5HT-2A/dopamine D2 receptors (Ereshefsky, 1996).
- **2)** Ziprasidone sulfoxide (major) (Prod Info Geodon(R), 2002ae; Prakash et al, 2000).
- **3)** Benzisothiazole sulphoxide (Prod Info Geodon(R), 2002ae).
- **4)** Benzisothiazole sulphone (Prod Info Geodon(R), 2002ae).
- **5)** S-methyldihydroziprasidone (Prod Info Geodon(R), 2002ae).
- **6)** Ziprasidone sulfone (Prakash et al, 2000).
- **7)** Oxindole acetic acid (Prakash et al, 2000).
- **8)** Benzisothiazole piperazine (Prakash et al, 2000).

2.3.4 Excretion

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

2.3.5 Elimination Half-life

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

2.3.6 Extracorporeal Elimination

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

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Ziprasidone Hydrochloride

a) Oral (Capsule)

1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Ziprasidone hydrochloride is not approved for the treatment of patients with dementia-related psychosis (Prod Info GEODON(R) oral capsules, IM injection, 2008).

2) Ziprasidone Mesylate

a) Intramuscular (Powder for Solution)

1) Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 times to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Ziprasidone mesylate is not approved for the treatment of patients with dementia-related psychosis (Prod Info GEODON(R) oral capsules, IM injection, 2008).

3.1 Contraindications

A) Ziprasidone Hydrochloride

1) cardiac arrhythmias, history (Prod Info GEODON(R) oral capsules, IM injection, 2008)

2) 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3) heart failure, uncompensated (Prod Info GEODON(R) oral capsules, IM injection, 2008)

4) hypersensitivity to ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2008)

5) myocardial infarction, acute and recent (Prod Info GEODON(R) oral capsules, IM injection, 2008)

6) QT prolongation history including congenital long QT syndrome (Prod Info GEODON(R) oral capsules, IM injection, 2008)

B) Ziprasidone Mesylate

1) cardiac arrhythmias, history (Prod Info GEODON(R) oral capsules, IM injection, 2007)

2) concomitant use 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3) heart failure, uncompensated (Prod Info GEODON(R) oral capsules, IM injection, 2008)
4) hypersensitivity to ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2008)
5) myocardial infarction, acute and recent (Prod Info GEODON(R) oral capsules, IM injection, 2008)
6) QT prolongation, history including congenital long QT syndrome (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3.2 Precautions

A) Ziprasidone Hydrochloride

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info GEODON(R) oral capsules, IM injection, 2008)
2) bradycardia; increased risk of torsades de pointes and/or sudden death (Prod Info GEODON(R) oral capsules, IM injection, 2008)
3) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info GEODON(R) oral capsules, IM injection, 2008)
4) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use); disruption of body temperature regulation has been reported with antipsychotic agents (Prod Info GEODON(R) oral capsules, IM injection, 2008)
5) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucose (Prod Info GEODON(R) oral capsules, IM injection, 2008)
6) esophageal dysmotility and aspiration may occur, use cautiously in patients at risk for aspiration pneumonia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
7) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
8) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) is a risk (Prod Info GEODON(R) oral capsules, IM injection, 2008)
9) hypokalemia or hypomagnesemia, preexisting; increased risk of torsades de pointes and/or sudden death (Prod Info GEODON(R) oral capsules, IM injection, 2008)
10) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
11) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotics drugs; immediately discontinue drug (Prod Info GEODON(R) oral capsules, IM injection, 2008)
12) priapism has been reported rarely (Prod Info GEODON(R) oral capsules, IM injection, 2008)
13) rash and/or urticaria have been reported, discontinue if associated with systemic illness (eg, elevated WBC counts) (Prod Info GEODON(R) oral capsules, IM injection, 2008)
14) seizure disorder, history, or conditions which lower the seizure threshold (Prod Info GEODON(R) oral capsules, IM injection, 2008)
15) tardive dyskinesia, potentially irreversible, may occur (Prod Info GEODON(R) oral capsules, IM injection, 2008)

B) Ziprasidone Mesylate

1) elderly patients with dementia-related psychosis (unapproved use); increased risk of death; most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia) (Prod Info GEODON(R) oral capsules, IM injection, 2008)
2) bradycardia; increased risk of torsades de pointes and/or sudden death (Prod Info GEODON(R) oral capsules, IM injection, 2008)
3) cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension and syncope (Prod Info GEODON(R) oral capsules, IM injection, 2008)
4) conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic use); disruption of body temperature regulation has been reported with antipsychotic agents (Prod Info GEODON(R) oral capsules, IM injection, 2008)
5) diabetes mellitus or risk factors for diabetes mellitus; increased risk of severe hyperglycemia; monitor blood glucose (Prod Info GEODON(R) oral capsules, IM injection, 2008)
6) esophageal dysmotility and aspiration may occur, use cautiously in patients at risk for aspiration pneumonia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
7) elderly patients, especially elderly women are at increased risk of tardive dyskinesia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
8) hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) is a risk (Prod Info GEODON(R) oral capsules, IM injection, 2008)
9) hypokalemia or hypomagnesemia, preexisting; increased risk of torsades de pointes and/or sudden death (Prod Info GEODON(R) oral capsules, IM injection, 2008)
10) increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia (Prod Info GEODON(R) oral capsules, IM injection, 2008)
11) neuroleptic malignant syndrome, potentially fatal, has been reported in association with antipsychotics drugs; immediately discontinue drug (Prod Info GEODON(R) oral capsules, IM injection, 2008)
12) priapism has been reported rarely (Prod Info GEODON(R) oral capsules, IM injection, 2008)
13) rash and/or urticaria have been reported, discontinue if associated with systemic illness (eg, elevated WBC

counts) (Prod Info GEODON(R) oral capsules, IM injection, 2008)
14) seizure disorder, history, or conditions which lower the seizure threshold; use caution (Prod Info GEODON (R) oral capsules, IM injection, 2008)
15) tardive dyskinesia, potentially irreversible, may occur (Prod Info GEODON(R) oral capsules, IM injection, 2008)

3.3 Adverse Reactions

Cardiovascular Effects

Dermatologic Effects

Endocrine/Metabolic Effects

Gastrointestinal Effects

Hepatic Effects

Musculoskeletal Effects

Neurologic Effects

Ophthalmic Effects

Psychiatric Effects

Reproductive Effects

Respiratory Effects

Other

3.3.1 Cardiovascular Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.1.A Ziprasidone Hydrochloride

Hypertension

Orthostatic hypotension

Prolonged QT interval

Syncope

Tachycardia

Torsades de pointes

3.3.1.A.1 Hypertension
a) Incidence: bipolar mania, 3%; schizophrenia, not reported (Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of hypertension reported in short-term trials of patients with bipolar mania was 3% for ziprasidone hydrochloride-treated subjects (n=279) versus 2% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.A.2 Orthostatic hypotension

a) Incidence: frequent (Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Postural hypotension has been reported in both premarketing and postmarketing oral ziprasidone hydrochloride use and may be dose-dependent (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.A.3 Prolonged QT interval

a) Incidence: 0.06%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) QT prolongation is dose-related. It is not yet known whether ziprasidone hydrochloride will cause torsades de pointes or increase the rate of sudden death. In clinical trials, oral ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with 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 out of 2988) of patients on ziprasidone hydrochloride compared with 0.23% (1 out of 440) patients on placebo. Ziprasidone was not suspected to have caused the QTc prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000).

3.3.1.A.4 Syncope

a) Incidence: 0.6%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) The rare occurrence of syncope has been reported during postmarketing use of ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.A.5 Tachycardia

a) Incidence: bipolar mania, not reported; schizophrenia, 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) In short-term trials, the incidence of tachycardia was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 1% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) 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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.A.6 Torsades de pointes

a) Incidence: rare(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Although the development of torsades de pointes, in the presence of other multiple confounding factors, has been observed during postmarketing use of ziprasidone, a causal relationship has not been confirmed. In premarketing studies, the development of torsades 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 torsades de pointes has yet to be determined (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) In a case report of a 28 year-old female, Q-T prolongation occurred separately during two hospital admissions, and asymptomatic non-sustained polymorphic ventricular tachycardia occurred during the second admission while using ziprasidone concurrently with other potentially arrhythmogenic medications (lithium, ciprofloxacin, fluconazole, fluoxetine, and trazodone). Upon discontinuation of

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

3.3.1.B Ziprasidone Mesylate

Hypertension

Orthostatic hypotension

Prolonged QT interval

Syncope

Tachycardia

Torsades de pointes

3.3.1.B.1 Hypertension

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Hypertension was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.B.2 Orthostatic hypotension

a) Incidence: up to 5%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Postural hypotension, reported in up to 5% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate, has also been observed during postmarketing use (Prod Info GEODON (R) oral capsules, IM injection, 2007).

3.3.1.B.3 Prolonged QT interval

a) In a study of the QT/QTc prolongation effects of intramuscular ziprasidone mesylate, the mean increase in QTc from baseline to time of maximum plasma concentration following two injections of intramuscular ziprasidone mesylate (20 mg then 30 mg, given four hours apart) was 4.6 msec and 12.8 msec following the first and second injections, respectively, compared to 6 msec and 14.7 msec for the first and second injections, respectively, of haloperidol (7.5 mg then 10 mg, given four hours apart). No patients experienced a QTc interval exceeding 500 msec in this study (Prod Info GEODON(R) oral capsules, IM injection, 2007).

b) QT prolongation is dose-related. It is not yet known whether ziprasidone mesylate will cause torsades de pointes or increase the rate of sudden death. In clinical trials, oral ziprasidone hydrochloride increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with 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 out of 2988) of patients on ziprasidone hydrochloride compared with 0.23% (1 out of 440) patients on placebo. Ziprasidone was not suspected to have caused the QTc prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000).

3.3.1.B.4 Syncope

a) Incidence: 0.6%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) The rare occurrence of syncope has been reported during postmarketing use of ziprasidone (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.B.5 Tachycardia

a) Tachycardia, reported in 2% of patients with schizophrenia during short-term oral placebo-controlled trials, has been reported in postmarketing ziprasidone use (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.1.B.6 Torsades de pointes

a) Incidence: rare(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Although the development of torsades de pointes, in the presence of other multiple confounding factors, has been observed during postmarketing use of ziprasidone, a causal relationship has not been confirmed. In premarketing studies, the development of torsades 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 torsades de pointes has yet to be determined (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.2 Dermatologic Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.2.A Ziprasidone Hydrochloride

3.3.2.A.1 Rash

a) Incidence: 5%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.2.B Ziprasidone Mesylate

Furunculosis

Injection site pain

Sweating symptom

3.3.2.B.1 Furunculosis

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Furunculosis was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.2.B.2 Injection site pain

a) Incidence: 7% to9%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Pain at the site of injection was reported in 7% to 9% of patients during short-term fixed-dose

intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.2.B.3 Sweating symptom

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Sweating was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3 Endocrine/Metabolic Effects

Ziprasidone

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.3.A Ziprasidone

3.3.3.A.1 Diabetes mellitus

See Drug Consult reference: ATYPICAL ANTIPSYCHOTIC AGENTS - EFFECT ON GLUCOSE AND RISK OF DIABETES

3.3.3.B Ziprasidone Hydrochloride

Diabetes mellitus

Hyperglycemia

Increased prolactin level

Metabolic syndrome

Weight gain

3.3.3.B.1 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 (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 re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3.B.2 Hyperglycemia

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 (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 re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3.B.3 Increased prolactin level

a) Ziprasidone, like other drugs that antagonize dopamine D2 receptors, have the potential ot increase prolactin levels; however, the clinical significance is unknown (Prod Info GEODON(R) oral capsules, IM injection, 2007). Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone (Anon, 1996a; Kerwin & Taylor, 1996a). The changes are transient and return to baseline

within 12 hours of ziprasidone administration (Miceli et al, 2000; Goff et al, 1998a).

3.3.3.B.4 Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.3.B.5 Weight gain

a) Incidence: 0.4%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Weight gain was reported in 0.4% and 0.4% of patients on ziprasidone-treated and placebo-treated patients, respectively (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) 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) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

d) Compared to other atypical antipsychotics in a systemic review, ziprasidone is associated with a low risk of weight gain (Kingsbury et al, 2001; Taylor & McAskill, 2000).

3.3.3.C Ziprasidone Mesylate

Diabetes mellitus

Hyperglycemia

Increased prolactin level

Metabolic syndrome

3.3.3.C.1 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 (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 re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3.C.2 Hyperglycemia

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 (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 re-testing. All patients receiving an atypical antipsychotic should be monitored for symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weakness), and should be given blood glucose tests if such symptoms are seen. In some patients, resolution of hyperglycemia has occurred with discontinuation of the atypical antipsychotic; in other cases, it has not (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.3.C.3 Increased prolactin level

a) Ziprasidone, like other drugs that antagonize dopamine D2 receptors, have the potential ot increase prolactin levels; however, the clinical significance is unknown (Prod Info GEODON(R) oral capsules, IM injection, 2007). Prolactin level increases are usually small and seen mainly with higher doses of ziprasidone (Anon, 1996a; Kerwin & Taylor, 1996a). The changes are transient and return to baseline within 12 hours of ziprasidone administration (Miceli et al, 2000; Goff et al, 1998a).

3.3.3.C.4 Metabolic syndrome

See Drug Consult reference: ANTIPSYCHOTIC AGENTS - METABOLIC SYNDROME

3.3.4 Gastrointestinal Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.4.A Ziprasidone Hydrochloride

Abdominal pain

Constipation

Diarrhea

Indigestion

Loss of appetite

Nausea

Vomiting

Xerostomia

3.3.4.A.1 Abdominal pain

a) Incidence: bipolar mania, not reported; schizophrenia, frequent(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Abdominal pain was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.2 Constipation

a) Incidence: bipolar mania, not reported; schizophrenia, 9%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) In short-term trials, the incidence of constipation was 9% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 8% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.3 Diarrhea

a) Incidence: bipolar mania and schizophrenia, 5%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) The incidence of diarrhea reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) versus 4% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).
c) In short-term trials, the incidence of diarrhea was 5% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 4% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.4 Indigestion

a) Incidence: bipolar mania, not reported; schizophrenia, 8%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) In short-term trials, the incidence of dyspepsia was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.5 Loss of appetite

a) Incidence: bipolar mania, not reported; schizophrenia, 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) In short-term trials, the incidence of anorexia was 2% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 1% for placebo-treated subjects (n=273). (Prod Info GEODON (R) oral capsules, IM injection, 2007).
c) Anorexia was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).
d) An analysis of four 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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.6 Nausea

a) Incidence: bipolar mania and schizophrenia, 10%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of nausea reported in short-term trials of patients with bipolar mania was 10% for ziprasidone hydrochloride-treated subjects (n=279) versus 7% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) In short-term trials, the incidence of nausea was 10% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.7 Vomiting

a) Incidence: bipolar mania, 5%; schizophrenia, frequent(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of vomiting reported in short-term trials of patients with bipolar mania was 5% for ziprasidone hydrochloride-treated subjects (n=279) versus 2% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Vomiting was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day and was one of the more common reasons given for study dropouts during the bipolar mania trials(Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.A.8 Xerostomia

a) Incidence: bipolar mania, 5%; schizophrenia, 4%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

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) versus 4% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) In short-term trials, the incidence of dry mouth was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

d) An analysis of four 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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B Ziprasidone Mesylate

Abdominal pain

Constipation

Diarrhea

Indigestion

Loss of appetite

Nausea

Vomiting

3.3.4.B.1 Abdominal pain

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Abdominal pain was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.2 Constipation

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Constipation was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.3 Diarrhea

a) Incidence: up to 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Diarrhea was reported in up to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.4 Indigestion
a) Incidence: 1% to 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Dyspepsia was reported in 1% to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.5 Loss of appetite
a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Anorexia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.6 Nausea
a) Incidence: 4% to 12%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Nausea was reported in 4% to 12% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.4.B.7 Vomiting
a) Incidence: up to 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) Vomiting was reported in up to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.6 Hepatic Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

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 (Brown et al, 1999; Citrome, 1997; Kerwin & Taylor, 1996a).
b) Two patients in a clinical trial of ziprasidone were discontinued because of abnormal laboratory results. One patient had elevated gamma-glutamyl transpeptidase (GGT) and serum glutamic-pyruvic transaminase (SGPT/ALT) after 7 days of treatment with ziprasidone 10 milligrams/day, and one patient showed elevations of both serum glutamic-oxaloacetic transaminase (SGOT/AST) and SGPT/ALT after 8 days of treatment with ziprasidone 40 milligrams/day. Both patients had elevated GGT values at baseline. At follow-up, all values had returned or were returning to normal (Goff et al, 1998a).

3.3.6.B Ziprasidone Mesylate

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

3.3.8 Musculoskeletal Effects

3.3.8.A Ziprasidone Hydrochloride

Myalgia

Rhabdomyolysis, following correction of hyponatremia secondary to psychogenic polydipsia

3.3.8.A.1 Myalgia
a) Incidence: bipolar mania, 2%; schizophrenia, frequent(Prod Info GEODON(R) oral capsules, IM injection, 2007)
b) The incidence of myalgia reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) versus 0% for placebo-treated patients (n=136)

(Prod Info GEODON(R) oral capsules, IM injection, 2007).
c) Myalgia was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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

a) Rhabdomyolysis, possibly complicated by ziprasidone therapy, was observed in one patient following the correction of hyponatremia secondary to psychogenic polydipsia. The 50-year-old Caucasian male had begun ziprasidone therapy (40 mg twice daily) for the treatment of chronic paranoid schizophrenia three weeks before presenting with hyponatremia secondary to psychogenic polydipsia. Following the discontinuation of ziprasidone and the correction of hyponatremia via sodium chloride 0.9% administration and oral water restriction, the man developed rhabdomyolysis secondary to hyponatremia correction which manifested as an unexplained increase in serum alanine and aspartate aminotransferase levels and total serum creatine kinase elevated to 67,259 International Units/L. Following resolution of rhabdomyolysis, ziprasidone therapy was reinitiated at a dose of 80 mg twice daily with no recurrence of increased serum creatine kinase levels. While the author notes that hyponatremia secondary to psychogenic polydipsia or its correction was most likely the primary cause of rhabdomyolysis in this patient, he also asserts that a review of the literature allows supposition that the development of rhabdomyolysis may have been complicated by the prior use of ziprasidone. The use of the Naranjo probability scale indicated a possible relationship between the use of ziprasidone and the subsequent development of rhabdomyolysis (Zaidi, 2005).

3.3.9 Neurologic Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.9.A Ziprasidone Hydrochloride

Akathisia

Asthenia

Disturbance in speech

Dizziness

Dystonia

Extrapyramidal disease

Headache

Insomnia

Neuroleptic malignant syndrome

Paresthesia

Seizure

Somnolence

Tardive dyskinesia

3.3.9.A.1 Akathisia

a) Incidence: bipolar mania, 10%; schizophrenia, 8%(Prod Info GEODON(R) oral capsules, IM

injection, 2008a)
b) The incidence of akathisia reported in short-term trials of patients with bipolar mania was 10% for ziprasidone hydrochloride-treated subjects (n=279) versus 5% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
c) In short-term trials, the incidence of akathisia was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 7% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
d) Akathisia was one of the more common reasons given for study dropouts during the bipolar mania trials (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.2 Asthenia
a) Incidence: bipolar mania, 6%; schizophrenia, 5%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) The incidence of asthenia reported in short-term trials of patients with bipolar mania was 6% for ziprasidone hydrochloride-treated subjects (n=279) versus 2% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
c) In short-term trials, the incidence of asthenia was 5% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 3% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.3 Disturbance in speech
a) Incidence: bipolar mania, 2%; schizophrenia, not reported(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
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) versus 0% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.4 Dizziness
a) Incidence: bipolar mania, 16%; schizophrenia, 8%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
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) versus 7% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
c) In short-term trials, the incidence of dizziness and lightheadedness was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 6% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
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 (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.5 Dystonia
a) 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, and/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. Males and younger age groups appear to be at greater risk for developing acute dystonia (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.6 Extrapyramidal disease
a) Incidence: bipolar mania, 31%; schizophrenia, 14%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) General
1) In clinical trial adverse effect reports for ziprasidone hydrochloride, the manufacturer defines extrapyramidal symptoms to collectively include the following: Extrapyramidal syndrome, hypertonia, dystonia, dyskinesia, hypokinesia, tremor, paralysis, and twitching (Prod Info GEODON (R) oral capsules, IM injection, 2008a).
2) 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) versus 12% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
3) In short-term trials, the incidence of extrapyramidal symptoms (EPS) was 14% among ziprasidone hydrochloride -treated schizophrenia subjects (n=702) versus 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
c) Hypertonia
1) Hypertonia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in

schizophrenia trials. Hypertonia was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

2) An analysis of four 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

d) Hypokinesia

1) Hypokinesia occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Hypokinesia was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).

e) Tremor

1) Tremor occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Tremor was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

2) 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

f) Twitching

1) Twitching occurred at a frequency of less than 10% in bipolar mania trials and less than 5% in schizophrenia trials. Twitching was frequently (occurred in at least 1 of 100 people) observed during premarketing schizophrenia clinical trial at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.A.7 Headache

a) Incidence: bipolar mania, 18%; schizophrenia, not reported(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) The incidence of headache reported in short-term trials of patients with bipolar mania was 18% for ziprasidone hydrochloride-treated subjects (n=279) versus 17% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.8 Insomnia

a) Incidence: rare(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Although no causal relationship has been established, rare postmarketing reports of insomnia with ziprasidone use have been observed (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.9 Neuroleptic malignant syndrome

a) Incidence: rare(Murty et al, 2002)

b) 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 intravenous hydration and electrolyte replacement (Murty et al, 2002).

3.3.9.A.10 Paresthesia

a) Incidence: frequent(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Paresthesia was frequently (occurred in at least 1 of 100 people) reported in oral ziprasidone hydrochloride-treated patients during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day, although causality was not determined (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.11 Seizure

a) Incidence: 0.4%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Seizures were reported in 0.4% of ziprasidone hydrochloride-treated patients during clinical trials, although confounding factors may have contributed to the occurrence in many of these cases (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.12 Somnolence

a) Incidence: bipolar mania, 31%; schizophrenia, 14%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) The incidence of somnolence reported in short-term trials of patients with bipolar mania was 31% for ziprasidone hydrochloride-treated subjects (n=279) versus 12% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

c) In short-term trials, the incidence of somnolence was 14% among ziprasidone hydrochloride-treated

schizophrenia subjects (n=702) versus 7% for placebo-treated subjects (n=273). The frequency of somnolence appears to be dose-dependent (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
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 (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.A.13 Tardive dyskinesia

a) The use of antipsychotic drugs, such as ziprasidone hydrochloride, is a risk factor for the development of tardive dyskinesia. 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008a).
b) Tardive dyskinesia developed in a 70-year-old woman nine weeks following the initiation of ziprasidone therapy (100 milligrams/day) for the treatment of major depression with mood-congruent psychotic features. Symptoms included repetitive, involuntary jaw and toe movements (Keck et al, 2004).

3.3.9.B Ziprasidone Mesylate

Akathisia

Asthenia

Disturbance in speech

Dizziness

Dystonia

Extrapyramidal disease

Headache

Insomnia

Paresthesia

Seizure

Somnolence

Tardive dyskinesia

3.3.9.B.1 Akathisia

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) Akathisia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.2 Asthenia

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) Asthenia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.3 Disturbance in speech

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)
b) Speech disorder was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.4 Dizziness

a) Incidence: 3% to 10%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Dizziness was reported in 3% to 10% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.5 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, and/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. Males and younger age groups appear to be at greater risk for developing acute dystonia (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.6 Extrapyramidal disease

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Extrapyramidal syndrome was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a). See Drug Consult reference: NEUROLEPTIC-INDUCED EXTRAPYRAMIDAL REACTIONS

3.3.9.B.7 Headache

a) Incidence: 3% to 13%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Headache was reported in 3% to 13% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.8 Insomnia

a) Incidence: up to 3%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Insomnia was reported in up to 3% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

c) Although no causal relationship has been established, postmarketing reports of insomnia with ziprasidone use have been observed (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.9 Paresthesia

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Paresthesia was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.10 Seizure

a) Incidence: 0.4%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Seizures were reported in 0.4% of ziprasidone mesylate-treated patients during clinical trials, although confounding factors may have contributed to the occurrence in many of these cases (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.11 Somnolence

a) Incidence: 8% to 20%(Prod Info GEODON(R) oral capsules, IM injection, 2008a)

b) Somnolence was reported in 8% to 20% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.9.B.12 Tardive dyskinesia

a) The use of antipsychotic drugs, such as ziprasidone mesylate, is a risk factor for the development of tardive dyskinesia. 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 (Prod Info GEODON(R) oral capsules, IM injection, 2008a).

3.3.10 Ophthalmic Effects

3.3.10.A Ziprasidone Hydrochloride

Abnormal vision

Oculogyric crisis

3.3.10.A.1 Abnormal vision

a) Incidence: bipolar mania, 6%; schizophrenia, 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

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) versus 3% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).
c) In short-term trials, the incidence of abnormal vision was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).
d) An analysis of four 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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.10.A.2 Oculogyric crisis

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

3.3.12 Psychiatric Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.12.A Ziprasidone Hydrochloride

At risk for suicide

Mania

3.3.12.A.1 At risk for suicide

a) Because an attempt at suicide is inherently possible in patients with a psychotic illness or bipolar disorder, high-risk patients on drug therapy should receive close supervision. Also, in order to reduce the risk of overdose, ziprasidone prescriptions should be written for the smallest quantity of capsules consistent with good patient management (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.12.A.2 Mania

a) Summary
1) There have been several case reports of mania/hypomania associated ziprasidone use, including reports during postmarketing use (Prod Info GEODON(R) oral capsules, IM injection, 2007; Brieger, 2004; Baldassano et al, 2003).
b) Hypomania developed in a 40-year-old man on two occasions following the initiation and reinitiation of ziprasidone therapy for the treatment bipolar schizoaffective disorder. Hypomania developed eight days after ziprasidone (100 milligrams (mg)/day) was initiated with ongoing venlafaxine (150 mg/day) and valproate (1200 mg/day) therapy. Symptoms included decreased need for sleep, recklessness, talkativeness, high self-esteem and racing thoughts. Ziprasidone was stopped on day 10 after a worsening of symptoms. However, 6 weeks later, the patient was restarted on ziprasidone treatment (120 mg/day) and again developed a hypomanic episode after eight days of treatment. A dysphoric mood rather than euphoric mood marked this episode and ziprasidone was again discontinued. Symptoms of hypomania resolved within 24 hours on both occasions (Brieger, 2004).
c) Four cases of mania related to the initiation of ziprasidone administration have been reported in bipolar patients. Three of the cases occurred in males 25, 26 and 45 years of age and the other case occurred in a 29-year-old female. In each case the patients were receiving multiple psychotropic medications prior to ziprasidone administration. Each patient received an initial ziprasidone dose of 20 milligrams (mg) twice a day. Manic symptoms occurred within 3 to 7 days in each of the male patients at this dosage. With the woman patient, ziprasidone dosage was increased to 100 mg/day over a period of 5 days and on the fifth day of treatment she developed manic symptoms. Within 3 to 7 days of dosage reduction or discontinuation of ziprasidone, all of the patient's manic symptoms improved. The authors speculated that ziprasidone's potent inhibition of noradrenergic and serotonergic reuptake sites may play a role in the observed switch from bipolar depression to mania (Baldassano et al, 2003).

3.3.12.B Ziprasidone Mesylate

Agitation

At risk for suicide

Personality disorder

3.3.12.B.1 Agitation

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Agitation was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.12.B.2 At risk for suicide

a) Because an attempt at suicide is inherently possible in patients with a psychotic illness or bipolar disorder, high-risk patients on drug therapy should receive close supervision (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.12.B.3 Personality disorder

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Personality disorder was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.14 Reproductive Effects

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.14.A Ziprasidone Hydrochloride

3.3.14.A.1 Priapism

a) Incidence: rare(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Although no causal relationship has been established, rare postmarketing reports of priapism with ziprasidone use have been observed and one case was reported during premarketing trials. Surgical intervention may be required in severe cases (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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

3.3.14.B Ziprasidone Mesylate

Dysmenorrhea

Priapism

3.3.14.B.1 Dysmenorrhea

a) Incidence: up to 2%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Dysmenorrhea was reported in up to 2% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.14.B.2 Priapism

a) Incidence: up to 1%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) Priapism, reported in up to 1% of patients during short-term fixed-dose intramuscular trials of ziprasidone mesylate, has also been observed during postmarketing use. Surgical intervention may be required in severe cases (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.15 Respiratory Effects

3.3.15.A Ziprasidone Hydrochloride

Cough

Dyspnea

Respiratory tract infection

Rhinitis

3.3.15.A.1 Cough

a) Incidence: bipolar mania, not reported; schizophrenia, 3%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) In short-term trials, the incidence of cough was 3% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 1% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.15.A.2 Dyspnea

a) Incidence: bipolar mania, 2%; schizophrenia, frequent(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) The incidence of dyspnea reported in short-term trials of patients with bipolar mania was 2% for ziprasidone hydrochloride-treated subjects (n=279) versus 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Dyspnea was frequently observed during premarketing schizophrenia clinical trials at multiple doses greater than 4 milligrams/day (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.15.A.3 Respiratory tract infection

a) Incidence: bipolar mania, not reported; schizophrenia, 8%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) In short-term trials, the incidence of respiratory tract infection was 8% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 3% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.15.A.4 Rhinitis

a) Incidence: bipolar mania, not reported; schizophrenia, 4%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

b) In short-term trials, the incidence of rhinitis was 4% among ziprasidone hydrochloride-treated schizophrenia subjects (n=702) versus 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) An analysis of four 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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3.3.16 Other

Ziprasidone Hydrochloride

Ziprasidone Mesylate

3.3.16.A Ziprasidone Hydrochloride

Accidental injury

Death

3.3.16.A.1 Accidental injury

a) Incidence: bipolar mania and schizophrenia, 4%(Prod Info GEODON(R) oral capsules, IM injection, 2007)

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) versus 1% for placebo-treated patients (n=136) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) In short-term trials, the incidence of accidental injuries was 4% among ziprasidone hydrochloride-

treated schizophrenia subjects (n=702) versus 2% for placebo-treated subjects (n=273) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

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 and 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 versus 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% confidence interval (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 was 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 (Gill et al, 2007).

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 and 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% confidence interval (CI), 1.39 to 1.56). In the multi-variable 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 multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

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

3.3.16.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 and 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 versus 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% confidence interval (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 was 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 (Gill et al, 2007).

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 and 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% confidence interval (CI), 1.39 to 1.56). In the multi-variable 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 multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study (Schneeweiss et al, 2007).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Geodon(R), 2002ad) (All Trimesters)

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

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

4) Literature Reports

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

B) Breastfeeding

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

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

2) Clinical Management

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

3) Literature Reports

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

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Acecainide

Ajmaline

Ajmaline

Amiodarone

Amisulpride

Amitriptyline

Amoxapine

Aprindine

Arsenic Trioxide

Arsenic Trioxide

Astemizole

Azimilide

Bepridil

Bretylium

Carbamazepine

Chloral Hydrate

Chloroquine

Chlorpromazine

Chlorpromazine

Cisapride

Clarithromycin

Desipramine

Disopyramide

Disopyramide

Dofetilide

Dolasetron

Doxepin

Droperidol

Enflurane

Erythromycin

Flecainide

Fluconazole

Fluoxetine

Foscarnet

Gatifloxacin

Gemifloxacin

Halofantrine

Haloperidol

Halothane

Hydroquinidine

Hydroquinidine

Ibutilide

Iloperidone

Imipramine

Isoflurane

Isradipine

Lapatinib

Levofloxacin

Levomethadyl

Lidoflazine

Lorcainide

Lumefantrine

Mefloquine

Mesoridazine

Mesoridazine

Methadone

Moxifloxacin

Nilotinib

Nortriptyline

Octreotide

Pentamidine

Pimozide

Pirmenol

Pirmenol

Prajmaline

Prajmaline

Probucol

Procainamide

Procainamide

Prochlorperazine

Prochlorperazine

Propafenone

Protriptyline

Quinidine

Ranolazine

Sematilide

Sertindole

Sotalol

Sparfloxacin

Spiramycin

Sultopride

Sunitinib

Tacrolimus

Tedisamil

Telithromycin

Terfenadine

Tetrabenazine

Tetrabenazine

Thioridazine

Trifluoperazine

Trifluoperazine

Trimipramine

Vasopressin

Zolmitriptan

Zotepine

3.5.1.A Acecainide

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

3.5.1.B Ajmaline

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

3.5.1.C Ajmaline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman,

2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

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

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

3.5.1.F Amitriptyline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.G Amoxapine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

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

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

3.5.1.J Arsenic Trioxide
1) Interaction Effect: prolongation of the QTc interval and/or torsades de pointes
2) Summary: Arsenic trioxide can prolong the QT interval in some patients, which may result in ventricular tachycardia, ventricular fibrillation, and torsades de pointes and should not be administered with other drugs that may prolong the QT interval (Prod Info Trisenox(R), 2001b). Several antipsychotic agents have

demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999a), haloperidol (O'Brien et al, 1999a), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999c), sertindole (Agelink et al, 2001b), quetiapine (Owens, 2001d), sultopride (Lande et al, 1992c), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of arsenic trioxide and antipsychotics is not recommended.
7) Probable Mechanism: additive effects on QTc prolongation
8) Literature Reports
a) QT/QTc prolongation should be expected during treatment with arsenic trioxide and torsade de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age (Prod Info Trisenox(R), 2001a).

3.5.1.K Astemizole

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

3.5.1.L Azimilide

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

3.5.1.M Bepridil

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002d; Agelink et al, 2001; Owens, 2001a; Prod Info Orap(R), 1999c; Prod Info Haldol(R), 1998). In U.S. clinical trials, bepridil increased QT and QTc intervals which was associated with torsades de pointes in approximately 1% of patients. Other drugs that increase the QT interval may exaggerate the prolongation of the QT interval observed with bepridil (Prod Info Vascor(R), 1997). Pimozide is contraindicated in patients taking other drugs which may prolong the QT interval (Prod Info Orap(R), 1999c).
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as bepridil, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.
7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999b).

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

3.5.1.N Bretylium

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and Class III antiarrhythmic agents is contraindicated.

7) Probable Mechanism: additive QT prolongation

8) Literature Reports

a) Concurrent use of class III antiarrhythmic agents, and other drugs that can prolong the QT interval, such as ziprasidone, is not recommended. Dofetilide should be stopped for at least 2 days before any interacting drug is initiated (Yamreudeewong et al, 2003).

3.5.1.O Carbamazepine

1) Interaction Effect: decreased ziprasidone plasma concentrations

2) Summary: Ziprasidone is metabolized primarily by CYP3A4. The concomitant use of carbamazepine (a CYP3A4 inducer) 200 mg twice daily for 21 days decreased the ziprasidone AUC by approximately 35%. Therefore, caution should be used when carbamazepine and ziprasidone are coadministered due to the potential for reduced ziprasidone plasma concentrations (Prod Info GEODON(R) oral capsules, IM injection, 2008).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Use caution when prescribing carbamazepine to a patient who takes ziprasidone. Concomitant use of carbamazepine and ziprasidone has resulted in decreased ziprasidone plasma concentrations (Prod Info GEODON(R) oral capsules, IM injection, 2008).

7) Probable Mechanism: induction of CYP3A4-mediated ziprasidone metabolism by carbamazepine

3.5.1.P Chloral Hydrate

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including chloral hydrate (Prod Info Geodon(TM), 2002k; Young et al, 1986).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and chloral hydrate is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.Q Chloroquine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including chloroquine (Prod Info Geodon(TM), 2002l). Chloroquine has been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Aralen(R), 1999).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and chloroquine is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.R Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001c), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.

7) Probable Mechanism: additive QT prolongation

3.5.1.S Chlorpromazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and phenothiazines is contraindicated (Prod Info Compazine(R), 2002a; Prod Info Geodon(R), 2002w).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: additive QT prolongation

3.5.1.T Cisapride

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Some antipsychotic agents prolong the QT interval and an additive effect would be anticipated if administered with other agents which lengthen the QT interval (Prod Info Geodon(TM), 2002c; Owens, 2001; Prod Info Orap(R), 1999a). Torsades de pointes and QT prolongation have been reported with cisapride (Prod Info Propulsid(R), 2000).

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of antipsychotics and agents that prolong the QT interval, such as cisapride, is contraindicated. In particular, pimozide is contraindicated in individuals with congenital QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which may prolong the QT interval.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999).

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

3.5.1.U Clarithromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including clarithromycin (Prod Info Geodon(TM), 2002s; Prod Info Biaxin(R), 2002).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and clarithromycin is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.V Desipramine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).

7) Probable Mechanism: additive cardiac effects

3.5.1.W Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.X Disopyramide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.Y Dofetilide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).

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

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

3.5.1.AA Doxepin
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

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

3.5.1.AC Enflurane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including enflurane (Prod Info Geodon(R), 2002o; Owens, 2001f).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as enflurane, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002n).

3.5.1.AD Erythromycin

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002t). Erythromycin significantly increased the mean QTc interval versus baseline in a retrospective study of 49 patients (Oberg & Bauman, 1995a). Erythromycin has demonstrated QTc prolongation in combination with other drugs that prolong the QT interval (Prod Info PCE(R), 1997).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as erythromycin, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) Erythromycin significantly increased the QTc interval compared with baseline in a retrospective study of 49 patients. The erythromycin dose was 500 milligrams or 1 gram four times daily, with a mean of 15 doses received. Patients (n equal to 9) who received 60 mg/kg/day or more all developed increases in QT interval of 15% or greater. For all patients, the mean QTc interval increased from 432 milliseconds (msec) at baseline to 483 msec (p less than 0.01). In patients with delayed repolarization at baseline (n equal to 9), the QTc interval increased from 473 msec to 525 msec (p less than 0.01). In patients with heart disease (n equal to 30), all experienced an increase in QTc interval (mean of 15%), compared with an increase of 8% in patients without heart disease (p less than 0.05). In 5 patients (10%), the QTc interval was severely prolonged. One patient developed torsades de pointes attributed to erythromycin. Of 16 patients receiving cotrimoxazole concomitantly, 8 developed QT prolongation of 15% or greater (Oberg & Bauman, 1995).

3.5.1.AE Flecainide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, the coadministration of Class I antiarrhythmics and other drugs known to prolong the QTc interval, such as ziprasidone is contraindicated (Prod Info Geodon(TM), 2002j; Prod Info Tambocor(R) flecainide acetate, 1998).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and Class I antiarrhythmic agents is contraindicated.

7) Probable Mechanism: additive cardiac effects

3.5.1.AF Fluconazole

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval (Prod Info Geodon(TM), 2002). Case reports have described QT prolongation and torsades de pointes associated with fluconazole

(Khazan & Mathis, 2002; Wassmann et al, 1999).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as fluconazole, is contraindicated.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002).

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

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

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

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

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

3.5.1.AK Halofantrine

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

3.5.1.AL Haloperidol

1) Interaction Effect: cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Haloperidol is associated with QTc prolongation and torsade de pointes (Hassaballa & Balk, 2003a; Prod Info Haldol(R), 2001). Coadministration of ziprasidone with drugs that potentially prolong the QTc interval, such as haloperidol, is contraindicated (Prod Info Geodon(R), 2002d).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with agents that prolong the QT interval, such as haloperidol, is contraindicated.
7) Probable Mechanism: additive effects on QT prolongation
8) Literature Reports

a) Seven patients developed torsade de pointes after therapeutic use of haloperidol in high doses. Three patients developed the dysrhythmia after administration of 211 milligrams (mg) to 825 mg haloperidol over 1 to 2 days for agitated delirium. These 3 patients recovered from the initial episodes, but 1 patient subsequently died of cardiac arrest upon readministration of haloperidol (Metzger & Friedman, 1993; Wilt et al, 1993). Torsades de pointes developed in 8 of 223 critically ill patients in intensive care units. Patients who received intravenous haloperidol greater than 35 mg/day or had a QTc interval prolongation of greater than 500 milliseconds were at greatest risk (Sharma et al, 1998).

b) Numerous case reports have described significant QTc prolongation and torsades de pointes (TdP) associated with haloperidol. Hemodynamically significant ventricular tachyarrhythmias, ventricular fibrillation, asystole, and death have been reported. The risk of TdP appears to be greater with intravenous haloperidol, but has occurred with oral and intramuscular use. The risk increases with doses greater than 35 milligrams (mg) over 24 hours, although TdP has been associated with a dose as low as 10 mg administered intravenously over 4 hours. To prevent haloperidol-induced TdP, screen patients for a history of dilated cardiomyopathy or alcohol abuse, testing for hypothyroidism before therapy, obtaining an electrocardiogram at baseline and throughout therapy, and monitoring potassium, magnesium, and calcium. In patients with a baseline QTc greater than 450 milliseconds (msec), haloperidol should be used cautiously or an alternative agent should be used. Discontinue haloperidol if the QTc increases more than 25% from baseline or if flattening of T-waves or development of U-waves occurs (Hassaballa & Balk, 2003).

c) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002c).

3.5.1.AM Halothane

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which may also prolong the QTc interval, including halothane (Prod Info Geodon(R), 2002ac; Owens, 2001j).
3) Severity: contraindicated
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as halothane, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias ((Anon, 2000)). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002ab).

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

3.5.1.AO Hydroquinidine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.AP Ibutilide
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: The manufacturer of ziprasidone states that concomitant use of ziprasidone and Class III antiarrhythmic agents is contraindicated (Prod Info Geodon(TM), 2002m). Bretylium should not be used with other drugs known to prolong the QTc interval , including ziprasidone (Yamreudeewong et al, 2003a).
3) Severity: contraindicated
4) Onset: unspecified

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

3.5.1.AQ Iloperidone
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when iloperidone and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec (Prod Info FANAPT(TM) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of iloperidone and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Iloperidone should be avoided in patients with significant cardiovascular illness, eg, cardiac arrhythmia, QT prolongation, recent acute myocardial infarction, and uncompensated heart failure. If concomitant use is necessary, consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels. Discontinue iloperidone in patients with persistent QTc measurements greater than 500 msec(Prod Info FANAPT(TM) oral tablets, 2009).
7) Probable Mechanism: additive effects on the QT interval
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

3.5.1.AR Imipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

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

3.5.1.AT Isradipine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Even though no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including isradipine (Prod Info Geodon(TM), 2002q; Prod Info DynaCirc(R), 2000).

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone with other agents that can prolong the QT interval, such as isradipine, is contraindicated.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(TM), 2002p).

3.5.1.AU Lapatinib

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

2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, caution should be used when lapatinib and drugs that prolong the QT interval are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008). Thirteen patients had either QTcF (corrected QT by the Friedericia method) greater than 480 msec or an increase in QTcF of greater than 60 msec in an uncontrolled, open-label, dose escalation study in advanced cancer patients (n=81) who received lapatinib doses ranging from 175 mg/day to 1800 mg/day, with serial ECGs collected on days 1 and 14 (Prod Info TYKERB oral tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of lapatinib and drugs that prolong the QT interval may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info TYKERB oral tablets, 2008).

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AV Levofloxacin

1) Interaction Effect: increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Although no formal drug interaction studies have been done, ziprasidone should not be coadministered with other drugs which are also known to prolong the QTc interval, including levofloxacin (Prod Info Geodon(R) Capsules & Geodon(R) for Injection, 2004; Prod Info Levaquin, 2004).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of ziprasidone and levofloxacin is not recommended.

7) Probable Mechanism: additive QT prolongation effects

3.5.1.AW Levomethadyl

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

2) Summary: Any drug known to have the potential to prolong the QT interval should not be used with levomethadyl. Possible pharmacodynamic interactions can occur between levomethadyl and potentially arrhythmogenic agents such as ziprasidone that prolong the QT interval (Prod Info Orlaam(R), 2001).

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Levomethadyl is contraindicated in patients being treated with ziprasidone as it may precipitate QT prolongation and interact with levomethadyl.

7) Probable Mechanism: additive cardiac effects

8) Literature Reports

a) It has been shown that ziprasidone prolongs the QTc and that this represents a risk of potentially fatal ventricular dysrhythmias (Anon, 2000). QT prolongation is dose-related. It is not yet known whether

ziprasidone will cause torsades de pointes or increase the rate of sudden death. In clinical trials ziprasidone increased the QTc interval, compared to placebo, by approximately 10 milliseconds (msec) at the highest dose (160 milligrams). Baseline QTc interval increased 9 to 14 msec more with ziprasidone than with risperidone, olanzapine, quetiapine, and haloperidol, but QTc interval was 14 msec less than that observed with thioridazine (Prod Info Geodon(R), 2002m).

3.5.1.AX Lidoflazine

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

3.5.1.AY Lorcainide

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

3.5.1.AZ Lumefantrine

1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on QT interval prolongation, concomitant use of artemether/lumefantrine with drugs that prolong the QT interval should be avoided (Prod Info COARTEM(R) oral tablets, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of artemether/lumefantrine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on QT interval prolongation (Prod Info COARTEM(R) oral tablets, 2009).
7) Probable Mechanism: additive effects on QT interval prolongation
8) Literature Reports
a) Concurrent administration of a single dose of IV quinine 10 mg/kg with the final dose of a 6-dose regimen of artemether/lumfantrine did not alter the systemic exposure to quinine, lumefantrine, or dihydroartemisinin (active metabolite of artemether). Although artemether exposure was decreased, it was not believed to be clinically significant. The effects on QT prolongation were not reported in this study (Prod Info COARTEM(R) oral tablets, 2009).

3.5.1.BA Mefloquine

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

3.5.1.BB Mesoridazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of mesoridazine states that concomitant use with

other drugs which prolong the QT interval is contraindicated (Prod Info Serentil(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999c), haloperidol (O'Brien et al, 1999c), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001g), risperidone (Duenas-Laita et al, 1999e), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992e), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics and mesoridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

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

3.5.1.BD Methadone
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Cases of QT interval prolongation and serious arrhythmias, including torsade de pointes, have been reported with methadone use (Prod Info DOLOPHINE(R) HYDROCHLORIDE oral tablets, 2006). Ziprasidone use is associated with dose-related QT interval prolongation. Due to the potential for additive effects on QT interval prolongation, concurrent use of methadone and ziprasidone is contraindicated (Prod Info GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, 2005).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of methadone and ziprasidone is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info GEODON(R) oral capsule, GEODON(R) intramuscular powder for solution, 2005).
7) Probable Mechanism: additive effects on QT interval prolongation

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

3.5.1.BF Nilotinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of nilotinib with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of nilotinib with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info TASIGNA(R) oral capsules, 2007).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BG Nortriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

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

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

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

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

3.5.1.BL Pirmenol
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).
c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

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

3.5.1.BN Prajmaline
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports
a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).
b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration (Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BO Probucol

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

3.5.1.BP Procainamide

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

3.5.1.BQ Procainamide

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Several antipsychotic agents have demonstrated QT prolongation including amisulpride, haloperidol, iloperidone, paliperidone, quetiapine, risperidone, sertindole, sultopride, ziprasidone, and zotepine (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Solian(R), 1999e; O'Brien et al, 1999d; Prod Info INVEGA(TM) extended-release oral tablets, 2006; Owens, 2001i; Duenas-Laita et al, 1999f; Agelink et al, 2001d; Lande et al, 1992f; Prod Info GEODON(R) intramuscular injection, oral capsule, 2005; Sweetman, 2003). Because Class IA antiarrhythmic agents may also prolong the QT interval and increase the risk of arrhythmias, the concurrent administration of antipsychotics with a drug from this class is not recommended (Prod Info FANAPT(TM) oral tablets, 2009; Prod Info Quinaglute(R), 1999).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and an antipsychotic is not recommended.
7) Probable Mechanism: additive cardiac effects
8) Literature Reports

a) In an open-label QTc study of patients with schizophrenia or schizoaffective disorder (n=160), iloperidone 12 mg twice a day was associated with QTc prolongation of 9 msec (Prod Info FANAPT(TM) oral tablets, 2009).

b) QRS widening, QTc interval prolongation, and torsades de pointes may occur with disopyramide therapy (Prod Info Norpace(R), 1997).

c) The effects of combined therapy with quinidine (Class IA antiarrhythmic agent) and haloperidol (antipsychotic agent) were studied by giving 12 healthy volunteers haloperidol 5 mg alone and with 250 mg of quinidine bisulfate. The study demonstrated significant increases in the plasma concentrations of haloperidol when given concurrently with quinidine versus haloperidol treatment alone. The mean area under the concentration curve (AUC) was increased from 54.3 ng/h/mL on haloperidol alone to 103.2 ng/h/mL on combined therapy. The peak concentration (Cmax) also showed an increase from 1.9 ng/mL on haloperidol to 3.8 ng/mL on combined therapy. Half-life (T1/2) and time to peak concentration

(Tmax) were not significantly changed, thereby suggesting to the authors that a tissue binding mechanism is more likely responsible for the plasma level changes than an elimination alteration (Young et al, 1993).

3.5.1.BR Prochlorperazine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001c), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

3.5.1.BS Prochlorperazine

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

3.5.1.BT Propafenone

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

3.5.1.BU Protriptyline

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

3.5.1.BV Quinidine

1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Even though no formal drug interaction studies have been done, the manufacturer of ziprasidone warns against its administration with other drugs which are also known to prolong the QTc

interval, including Class IA antiarrhythmic agents (Prod Info Geodon(R), 2002j).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of a Class IA antiarrhythmic and ziprasidone is contraindicated.
7) Probable Mechanism: additive cardiac effects

3.5.1.BW Ranolazine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Treatment with ranolazine has been associated with QTc prolongation (Prod Info RANEXA(R) extended-release oral tablets, 2008). Ziprasidone use is associated with dose-related QT interval prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2008). Concurrent use of ranolazine and ziprasidone is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of ranolazine and ziprasidone is contraindicated due to the potential for additive effects on QT interval prolongation (Prod Info GEODON(R) oral capsules, IM injection, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

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

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

3.5.1.BZ Sotalol

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

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

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

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

3.5.1.CD Sunitinib
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Sunitinib has been associated with prolongation of the QT interval in a dose dependent manner, with torsade de pointes occurring in less than 0.1% patients exposed to sunitinib. Due to the potential for additive effects on the QT interval and increased risk for torsade de pointes, caution should be used when sunitinib and ziprasidone are given concomitantly. Consideration should be given to monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium)

levels (Prod Info SUTENT(R) oral capsules, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of sunitinib and ziprasidone may result in additive effects on the QT interval and an increased risk of torsade de pointes. Therefore, caution should be used when these agents are given concomitantly. Consider monitoring cardiac function periodically with on-treatment ECGs and evaluating electrolyte (ie, magnesium, potassium) levels (Prod Info SUTENT(R) oral capsules, 2008).
7) Probable Mechanism: additive effects on the QT interval

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

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

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

3.5.1.CH Terfenadine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Some antipsychotics have been shown to prolong the QTc interval at the recommended therapeutic dose (Prod Info Geodon(TM), 2002aa; Owens, 2001k; Prod Info Orap(R), 1999e). Even though no formal drug interaction studies have been done, the coadministration of terfenadine and other drugs known to prolong the QTc interval, including antipsychotics, is contraindicated (Anon, 1997).
3) Severity: contraindicated

4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of terfenadine with any drug that prolongs the QT interval, such as antipsychotic agents, is contraindicated.
7) Probable Mechanism: additive effect on QT interval
8) Literature Reports
a) Electrocardiographic changes that have occurred during clinical trials with pimozide have included prolongation of the corrected QT interval, flattening, notching, and inversion of the T wave and the appearance of U waves. In experimental studies, sudden, unexpected deaths have occurred while patients were receiving pimozide doses of 1 mg/kg. The proposed mechanism for these deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmias (Prod Info Orap(R), 1999d).

3.5.1.CI Tetrabenazine
1) Interaction Effect: an increased risk of QT interval prolongation
2) Summary: Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, concomitant use of tetrabenazine with drugs that prolong the QT interval should be avoided. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval (Prod Info XENAZINE(R) oral tablets, 2008).
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CJ Tetrabenazine
1) Interaction Effect: increased risk of QT interval prolongation
2) Summary: Tetrabenazine causes a small increase in the corrected QT interval. As the degree of prolongation increases, QT prolongation can develop into torsade de pointes-type VT. The concomitant use of tetrabenazine with other drugs known for QT prolongation (eg, ziprasidone) should be avoided (Prod Info XENAZINE(R) oral tablets, 2008). In a randomized, double-blind, placebo controlled crossover study of healthy subjects, the effect of a single 25 mg or 50 mg dose of tetrabenazine on the QT interval was studied with moxifloxacin as a positive control. The 50 mg dose of tetrabenazine caused an approximate 8 millisecond mean increase in QT (Prod Info XENAZINE(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of tetrabenazine with ziprasidone or other drugs that prolong the QT interval should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes (Prod Info XENAZINE(R) oral tablets, 2008). However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CK Thioridazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Although citing no data, the manufacturer of thioridazine states that concomitant use with other drugs which prolong the QT interval is contraindicated (Prod Info Mellaril(R), 2001). Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999b), haloperidol (O'Brien et al, 1999b), pimozide (Prod Info Orap(R), 2000), quetiapine (Owens, 2001e), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), risperidone (Duenas-Laita et al, 1999d), sertindole (Agelink et al, 2001c), sultopride (Lande et al, 1992d), ziprasidone (Prod Info GEODON (R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2004).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as antipsychotics, and thioridazine, is contraindicated.
7) Probable Mechanism: additive QT prolongation

3.5.1.CL Trifluoperazine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac

arrest)
2) Summary: Concomitant use of phenothiazines and antipsychotic agents may cause additive effects on the QT interval and is not recommended. Q and T wave distortions have been observed in patients taking phenothiazines (Prod Info Compazine(R), 2002; Prod Info Stelazine(R), 2002; Prod Info Thorazine(R), 2002). Other phenothiazines may have similar effects, though no reports are available. Several antipsychotic agents have demonstrated QT prolongation including amisulpride (Prod Info Solian(R), 1999), haloperidol (O'Brien et al, 1999), paliperidone (Prod Info INVEGA(TM) extended-release oral tablets, 2006), quetiapine (Owens, 2001c), risperidone (Duenas-Laita et al, 1999b), sertindole (Agelink et al, 2001a), sultopride (Lande et al, 1992), ziprasidone (Prod Info GEODON(R) intramuscular injection, oral capsule, 2005), and zotepine (Sweetman, 2003).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of agents that prolong the QT interval, such as phenothiazines and antipsychotics, is not recommended.
7) Probable Mechanism: additive QT prolongation

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

3.5.1.CN Trimipramine
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)
2) Summary: Ziprasidone use is associated with dose-related prolongation of the QTc interval. Even though no formal drug interaction studies have been done, it is recommended that concurrent use with other agents that may prolong QTc interval be avoided (Prod Info GEODON(R) oral capsules, IM injection, 2007; Marshall & Forker, 1982).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for additive QTc interval prolongation, avoid the concurrent administration of ziprasidone and agents that can prolong the QTc interval (Prod Info GEODON(R) oral capsules, IM injection, 2007).
7) Probable Mechanism: additive cardiac effects

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

3.5.1.CP Zolmitriptan
1) Interaction Effect: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest)

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

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

4.0 Clinical Applications

Monitoring Parameters

Patient Instructions

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters
A) Ziprasidone Hydrochloride
1) Therapeutic
a) Physical Findings
1) Improvement of psychotic symptomatology (positive, negative symptoms) (Prod Info GEODON(R) oral capsules, IM injection, 2007).
2) Toxic
a) Laboratory Parameters
1) Torsade de Pointes
a) Ziprasidone may prolong the QT interval in some patients; ECG changes, blood pressure and heart rate monitoring may be warranted (Prod Info GEODON(R) oral capsules, IM injection, 2007).
b) Patients with hypokalemia or hypomagnesemia have an increased risk of the occurrence of torsade de pointes. Serum potassium and magnesium levels, at baseline and during ziprasidone

therapy, should be monitored for patients on concomitant diuretics or at risk for electrolyte disturbances (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Further evaluation, such as Holter monitoring, should be initiated for any patient who experiences symptoms during ziprasidone therapy that may indicate the development of torsade de pointes (eg dizziness, palpitations, syncope) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Diabetes Mellitus

a) Atypical antipsychotics, such as ziprasidone, have been linked with the development of hyperglycemia, some cases extreme and associated with ketoacidosis or hyperosmolar coma or death. Patients diagnosed with or at risk of diabetes mellitus should be monitored regularly for worsening of glucose control (eg fasting blood glucose, polydipsia, polyuria, polyphagia, weakness) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

b) Physical Findings

1) Tardive Dyskinesia

a) Patients being treated with antipsychotics, such as ziprasidone, may develop tardive dyskinesia. Severity and reversibility appear to be related to the duration of treatment and total cumulative dose administered, but may occur after brief treatment periods at low doses. The development of signs and symptoms of tardive dyskinesia should be monitored (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Neuroleptic Malignant Syndrome

a) The development of Neuroleptic Malignant Syndrome (NMS) has been associated with antipsychotic therapy. Patients taking ziprasidone should be monitored for signs and symptoms of NMS (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3) Body Temperature Dysregulation

a) Antipsychotics have been associated with disrupting the body's ability to regulate core body temperature. Patients taking ziprasidone should be monitored for changes in body temperature and dehydration (Prod Info GEODON(R) oral capsules, IM injection, 2007).

B) Ziprasidone Mesylate

1) Therapeutic

a) Physical Findings

1) Improvement of psychotic symptomatology (positive, negative symptoms) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Toxic

a) Laboratory Parameters

1) Torsade de Pointes

a) Ziprasidone may prolong the QT interval in some patients; ECG changes, blood pressure and heart rate monitoring may be warranted (Prod Info GEODON(R) oral capsules, IM injection, 2007).

b) Patients with hypokalemia or hypomagnesemia have an increased risk of the occurrence of torsade de pointes. Serum potassium and magnesium levels, at baseline and during ziprasidone therapy, should be monitored for patients on concomitant diuretics or at risk for electrolyte disturbances (Prod Info GEODON(R) oral capsules, IM injection, 2007).

c) Further evaluation, such as Holter monitoring, should be initiated for any patient who experiences symptoms during ziprasidone therapy that may indicate the development of torsade de pointes (eg dizziness, palpitations, syncope) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Diabetes Mellitus

a) Atypical antipsychotics, such as ziprasidone, have been linked with the development of hyperglycemia, some cases extreme and associated with ketoacidosis or hyperosmolar coma or death. Patients diagnosed with or at risk of diabetes mellitus should be monitored regularly for worsening of glucose control (eg fasting blood glucose, polydipsia, polyuria, polyphagia, weakness) (Prod Info GEODON(R) oral capsules, IM injection, 2007).

b) Physical Findings

1) Tardive Dyskinesia

a) Patients being treated with antipsychotics, such as ziprasidone, may develop tardive dyskinesia. Severity and reversibility appear to be related to the duration of treatment and total cumulative dose administered, but may occur after brief treatment periods at low doses. The development of signs and symptoms of tardive dyskinesia should be monitored (Prod Info GEODON(R) oral capsules, IM injection, 2007).

2) Neuroleptic Malignant Syndrome

a) The development of Neuroleptic Malignant Syndrome (NMS) has been associated with antipsychotic therapy. Patients taking ziprasidone should be monitored for signs and symptoms of NMS (Prod Info GEODON(R) oral capsules, IM injection, 2007).

3) Body Temperature Dysregulation

a) Antipsychotics have been associated with disrupting the body's ability to regulate core body temperature. Patients taking ziprasidone should be monitored for changes in body temperature and dehydration (Prod Info GEODON(R) oral capsules, IM injection, 2007).

4.2 Patient Instructions

A) Ziprasidone (By mouth)
Ziprasidone

Treats schizophrenia and certain problems caused by bipolar disorder.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to ziprasidone, or if you have severe heart failure or have recently had a heart attack. You should not use this medicine if you have a history of heart rhythm problems such as QT prolongation (including congenital long QT syndrome) or if you are using certain medicines that prolong the QT interval in the heart (such as dofetilide, sotalol, quinidine, disopyramide, procainamide, amiodarone, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus). This medicine should not be used in elderly patients who have a mental illness called dementia-related psychosis.

How to Use This Medicine:
Capsule
Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.
It is best to take this medicine with food or milk at the same time every day. Swallow the capsule whole. Do not break, crush, or chew it.
Keep using this medicine for the full treatment time, even if you feel better after the first few doses.

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

How to Store and Dispose of This Medicine:
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.
Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using medicines to lower blood pressure, such as atenolol, lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®. Tell your doctor if you are using diuretics or water pills (such as furosemide, Aldactazide®, Aldactone®, Dyazide®, Lasix®, Moduretic®, or Maxzide®), levodopa, carbamazepine (Carbatrol®, Tegretol®), or ketoconazole (Nizoral®).
Tell your doctor if you are also using levodopa (such as Dopart® or Larodopa®) or medicines such as bromocriptine (Parlodel®), Pramipexole (Mirapex®), ropinirole (Requip®), cabergoline (Dostinex®), or apomorphine (Apokyn®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart problems, liver disease, Alzheimer's disease, trouble with swallowing, or dizziness or fainting problems. Tell your doctor if you have a history of stroke, seizures, breast cancer, or low potassium or magnesium levels in your blood.
Make sure your doctor knows if you have thoughts of hurting yourself. Tell your doctor if you or anyone in your family has a history of diabetes.
Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndrome. Tell your doctor if you have ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Call your doctor if you are having signs of tardive dyskinesia such as rapid, worm-like movements of the tongue, or other uncontrolled movements of the mouth, tongue, cheeks, jaw, or arms and legs.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are using medicine for diabetes, your doctor may need to change your dose.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the

approved uses of this medicine.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. This medicine may also make you feel lightheaded when you get up suddenly from a lying or sitting position, so get up slowly.
This medicine might reduce how much you sweat. Your body could get too hot if you do not sweat enough. If your body gets too hot, you might feel dizzy, weak, tired, or confused. You might vomit or have an upset stomach. Do not get too hot while you are exercising. Avoid places that are very hot. Call your doctor if you are too hot and cannot cool down.
Your doctor will need to check your progress at regular visits while you are using this medicine. Be sure to keep all appointments.
Some side effects are more likely to happen in elderly people who have memory problems or other reduced mental skills. Make sure the doctor knows if the person who will be using this medicine has Alzheimer's disease or similar problems (often called "dementia").

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Chest pain.
Fast, slow, irregular (uneven), or pounding heartbeat.
Fever, sweating, confusion, muscle stiffness.
In males: Painful, prolonged erection of your penis.
Increase in thirst, hunger, or urination.
Lightheadedness, dizziness, or fainting.
Problems with balance or walking.
Seizures.
Severe diarrhea, nausea, vomiting, or stomach pain.
Skin rash.
Trouble swallowing or talking, sticking out of the tongue, or spasm of neck muscles.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:
Anxiety or restlessness.
Changes in vision.
Constipation or upset stomach.
Dry mouth.
Headache.
Sleepiness or unusual drowsiness.
Sneezing, cough, or runny or stuffy nose.
Tiredness.
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 (excessive movement, tension, or anxiety) in a person who has schizophrenia.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to ziprasidone, or if you have severe heart failure or have recently had a heart attack. You should not use this medicine if you have a history of heart rhythm problems such as QT prolongation (including congenital long QT syndrome) or if you are using certain medicines that prolong the QT interval in the heart (such as dofetilide, sotalol, quinidine, disopyramide, procainamide, amiodarone, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus). This medicine should not be used in elderly patients who have a mental illness called dementia-related psychosis.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are using medicines to lower blood pressure, such as atenolol, lisinopril,

metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, or Zestril®. Tell your doctor if you are using diuretics or water pills (such as furosemide, Aldactazide®, Aldactone®, Dyazide®, Lasix®, Moduretic®, or Maxzide®), levodopa, carbamazepine (Carbatrol®, Tegretol®), or ketoconazole (Nizoral®).
Tell your doctor if you are using levodopa (such as Dopart® or Larodopa®) or medicines such as bromocriptine (Parlodel®), Pramipexole (Mirapex®), ropinirole (Requip®), cabergoline (Dostinex®), or apomorphine (Apokyn®).
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart problems, liver disease, Alzheimer's disease, trouble with swallowing, or dizziness or fainting problems. Tell your doctor if you have a history of stroke, seizures, breast cancer, or low potassium or magnesium levels in your blood.
Tell your doctor if you or anyone in your family has a history of diabetes.
Make sure your doctor knows if you have a family history of a heart condition called congenital long QT syndrome. Tell your doctor if you have ever had Neuroleptic Malignant Syndrome (NMS) caused by other antipsychotic medicines.
Tardive dyskinesia (a movement disorder) may occur and may not go away after you stop using the medicine. Call your doctor if you are having signs of tardive dyskinesia such as rapid, worm-like movements of the tongue, or other uncontrolled movements of the mouth, tongue, cheeks, jaw, or arms and legs.
This medicine is not approved to treat behavior disorders in older people who have dementia. Using this medicine to treat this problem could increase the risk of death. This risk has not been shown for the approved uses of this medicine.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. This medicine may also make you feel lightheaded when you get up suddenly from a lying or sitting position, so get up slowly.
This medicine may cause an increase in your blood sugar. If you have diabetes, you may need to check your blood sugar more often. If you are taking medicine for diabetes, your doctor may need to change your dose.
This medicine may cause you to become overheated more easily than usual. Be careful when exercising, or when you are outdoors in hot or humid weather.
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Anxiety, agitation, trouble sleeping, or changes in mood or behavior.
Fast, slow, uneven, or pounding heartbeat.
Fever, sweating, confusion, muscle stiffness.
In males: painful, prolonged erection of your penis.
Increase in thirst, hunger, or urination.
Lightheadedness, dizziness, or fainting.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Problems with balance or walking.
Red or black stools.
Seizures.
Severe diarrhea, nausea, vomiting, or stomach pain.
Skin rash.
Trouble swallowing or talking, sticking out of the tongue, or spasm of neck muscles.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).

If you notice these less serious side effects, talk with your doctor:
Headache.
Pain where the shot was given.
Sleepiness or unusual drowsiness.
Sneezing, cough, or stuffy nose.
Tiredness.

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

4.3 Place In Therapy

A) Ziprasidone

1) 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 was 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 (Ray et al, 2009). 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 (Schneeweiss & Avorn, 2009).

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

3) 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).

B) Ziprasidone Hydrochloride

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

C) Ziprasidone Mesylate

See Drug Consult reference: FIRST- VS SECOND-GENERATION ANTIPSYCHOTIC AGENTS FOR SCHIZOPHRENIA

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Atypical antipsychotic (benzisothiazoyl piperazine derivative); serotonin (5HT)-2A/dopamine D2 antagonist. Also a 5HT-1A agonist (property may confer greater protection against adverse extrapyramidal effects) (Kerwin & Taylor, 1996; Bench et al, 1993; Fischman et al, 1996; Owens, 1996; Lieberman, 1993; Pickar, 1995; Anon, 1996a; Schotte et al, 1996).

2) Modest-to-low affinity for alpha-1, H1 receptors (Kerwin & Taylor, 1996). Inhibits norepinephrine reuptake (Pickar, 1995; Seeger et al, 1995).

3) In vitro: ratio of 5HT-2A/dopamine D2 receptor affinity greater than clozapine (2-fold), haloperidol (680-fold) (Seeger et al, 1995).

B) REVIEW ARTICLES

1) Focus on Ziprasidone (Green B, 2001).

2) Treatment of schizophrenia (includes use of atypical agents) (Marder, 1996; Fleischhacker, 1995; Meltzer et al, 1994; Lieberman, 1996; Weiden et al, 1996; Jeste et al, 1996).

3) Psychosis in mania (use of atypical agents) (McElroy et al, 1996).

4) Mechanism of action with respect to neurotransmitter pathways in the brain utilized by atypical antipsychotics, including ZIPRASIDONE (Kendrick, 1999).

5) A brief introductory review of ziprasidone is available (Tandon, 2000).

4.5 Therapeutic Uses

Ziprasidone

Ziprasidone Hydrochloride

Ziprasidone Mesylate

4.5.A Ziprasidone

4.5.A.1 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.B Ziprasidone Hydrochloride

Bipolar I disorder, acute manic or mixed episodes

Major depressive disorder, Treatment-resistant; Adjunct

Schizoaffective disorder

Schizophrenia

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

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of acute manic or mixed episodes in patients with bipolar disorder, with or without psychotic features (Prod Info GEODON(R) oral capsules, IM injection, 2007)

c) Adult:

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

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

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

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

c) Adult:

1) Ziprasidone augmentation of selective serotonin reuptake inhibitor (SSRI) therapy may be an effective option for patients with treatment- resistant major depression. In a prospective, open-label trial (n=20), patients with major depressive disorder resistant to SSRI therapy and a Hamilton Rating Scale for Depression (HAM-D) score of at least 14 received ziprasidone (initial, 20 milligrams (mg) twice daily, titrated in 20 mg/week increments to a maximum of 80 mg twice daily; mean dose, 82.1 mg/day) in addition to continued SSRI therapy with citalopram, fluoxetine, paroxetine, or sertraline for 6 weeks. At endpoint, 10 (50%) patients achieved response (defined as at least a 50% reduction in the HAM-D score from baseline to endpoint) and 5 (25%) patients achieved remission (defined as a HAM-D score of 7 or less at endpoint). Overall, the mean HAM-D score was reduced from 21.8 to approximately 12

from baseline to week 6, respectively. The most common adverse events included fatigue (50%), sleep disturbance (30%), restlessness (15%), tremor (15%), bruxism (15%), headache (10%), dry mouth (20%), gastrointestinal distress (20%), and urinary frequency (10%). No patient had a QTc interval greater than 500 milliseconds; however, a QTc interval increase of 30 milliseconds was observed in two patients. Placebo-controlled trials are needed to clarify the efficacy of ziprasidone augmentation therapy in SSRI-resistant depression (Papakostas et al, 2004).

4.5.B.3 Schizoaffective disorder

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

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

c) Adult:

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

4.5.B.4 Schizophrenia

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Positive/negative symptom improvement (Reeves & Harrigan, 1996; Harrigan et al, 1996a; Citrome, 1997a; Kerwin & Taylor, 1996b; Anon, 1996b)
Relatively low incidence of extrapyramidal symptoms (Reeves & Harrigan, 1996; Harrigan et al, 1996a; Citrome, 1997a; Kerwin & Taylor, 1996b; Anon, 1996b)
Causes more QT/QTc prolongation than risperidone, olanzapine, quetiapine, and haloperidol (Prod Info GEODON(R) oral capsules, IM injection, 2007)
Decreased the rate of relapse in patients with chronic, stable schizophrenia (Arato et al, 2002; Prod Info GEODON(R) oral capsules, IM injection, 2007)

c) Adult:

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

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

3) With 80/160 milligrams (mg) daily (6 weeks): reduction in Positive and Negative Syndrome Scale

(PANSS) total scores by 12.4/17.1 (-5.4 with placebo), negative subscale scores by 3.2/3.9 (-0.9 with placebo); significant improvement in BPRSd total score (18-item Brief Psychiatric Rating Scale derived from PANSS) (Reeves & Harrigan, 1996).

4) Ziprasidone was significantly superior to placebo in both time to relapse and rate of relapse, with no significant difference between the 2 dose groups in a 52-week, placebo-controlled trial (n = 294). Inpatients were randomized to receive ziprasidone 20 milligrams (mg) twice daily, 40 mg twice daily, 80 mg twice daily or placebo (Prod Info GEODON(R) oral capsules, IM injection, 2007).

4.5.C Ziprasidone Mesylate

4.5.C.1 Agitation, acute - Schizophrenia

FDA Labeled Indication

a) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intramuscular ziprasidone mesylate is effective for the treatment of acute agitation in schizophrenic patients (Prod Info GEODON(R) oral capsules, IM injection, 2007)

c) Adult:

1) 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 (Prod Info GEODON(R) oral capsules, IM injection, 2007).

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine

Haloperidol

Olanzapine

Perphenazine

Quetiapine

Risperidone

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia

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

4.6.B Haloperidol

Chronic schizophrenia

Schizophrenic episode, acute

4.6.B.1 Chronic schizophrenia

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

4.6.B.2 Schizophrenic episode, acute

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

b) Ziprasidone 160 milligrams (mg) and haloperidol 15 mg were both effective in improving overall psychopathology in patients with an acute exacerbation of schizophrenia or schizoaffective disorder (Goff et al, 1998). In a double-blind, dose-ranging study, patients received either haloperidol 15 mg/day (n=17), or ziprasidone 4 mg (n=19), ziprasidone 10 mg (n=17), ziprasidone 40 mg (n=17), or ziprasidone 160 mg (n=20). Despite 46 patients failing to complete the study, intention-to-treat analysis showed a trend toward significance for the ziprasidone dose response on the Brief Psychiatric Rating scale (p=0.08) and a statistically significant dose response for the Clinical Global Impression (CGI) scale (p less than 0.001). Changes in the CGI severity score were significantly changed from baseline as compared to the ziprasidone 4 mg group for both the haloperidol group (p less than 0.01) and the ziprasidone 160 mg group (p=0.001). Study termination was due to 18 patients having a lack of efficacy (4 in the haloperidol group), 7 due to liver transaminase elevations in ziprasidone groups, and 23 for unrelated reasons.

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

4.6.C Olanzapine

Chronic schizophrenia

Schizophrenia

4.6.C.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to

discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.C.2 Schizophrenia

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

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

4.6.D Perphenazine

4.6.D.1 Chronic schizophrenia

a) When newer antipsychotic medications (olanzapine, quetiapine, risperidone, and ziprasidone) were compared with the first-generation antipsychotic, perphenazine, the majority of patients in each group discontinued their antipsychotic study medication before 18 months. Patients (n=1493) with chronic schizophrenia were randomized to receive olanzapine 7.5 to 30 milligrams/day (mg/day), perphenazine 8 to 32 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6.0 mg/day, or ziprasidone 40 to 160 mg/day for up to 19 months. Overall, 74% of patients discontinued treatment for any cause before 18 months; discontinuation rates ranged from 64 to 82%. Time to discontinuation ranged from 3.5 months for ziprasidone to 9.2 months with olanzapine. The time to discontinuation was significantly longer in the olanzapine group as compared with the quetiapine (hazard ratio (HR), 0.63; 95% confidence interval (CI), 0.52 to 0.76; p less than 0.001) or risperidone groups (HR, 0.75; 95% CI, 0.62 to 0.90; p=0.002). Time to

discontinuation due to adverse events were similar between all groups, but the rates ranged from 10% for risperidone to 19% for olanzapine (p=0.04). More patients discontinued olanzapine due to greater weight gain (average of 0.9 kilograms/month) and greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides (Lieberman et al, 2005).

4.6.E Quetiapine

4.6.E.1 Chronic schizophrenia

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

4.6.F Risperidone

4.6.F.1 Chronic schizophrenia

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

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