

DRUGDEX-EV 2798

MICROMEDEX

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ASENAPINE

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0.0] Overview

1] Class

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

Antipsychotic

2] Dosing Information

a)] Adult

1)] switching from other antipsychotics; minimize the period of overlapping therapies [1]

a)] Bipolar I disorder, Acute mixed or [manic episodes](#)

1)] monotherapy, 10 mg SUBLINGUALLY twice a day; may decrease to 5 mg twice daily if there are adverse events; MAX 10 mg twice daily [1]

2)] adjunctive therapy, 5 mg SUBLINGUALLY twice a day with either lithium or valproate; may increase to 10 mg twice daily based on clinical response; MAX 10 mg twice daily [1]

b)] [Schizophrenia](#), Acute treatment

1)] 5 mg SUBLINGUALLY twice a day; MAX 10 mg twice daily [1]

b)] Pediatric

1)] [safety and effectiveness in pediatric patients have not been established \[1\]](#)

3] Contraindications

a)] hypersensitivity to the product [6]

4) Serious Adverse Effects

- a) [Angioedema](#)
- b) [Hypersensitivity reaction](#)
- c) [Neuroleptic malignant syndrome](#)
- d) Prolonged QT interval

5) Clinical Applications**a) FDA Approved Indications**

- 1) Bipolar I disorder, Acute mixed or [manic episodes](#)
- 2) [Schizophrenia](#), Acute treatment

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

Asenapine

C) Physicochemical Properties**1) Molecular Weight**

- a) 401.84; free base: 285.8 [2]

1.2] Storage and Stability**A) Preparation****1) Sublingual route**

- a) To ensure optimal absorption of the asenapine sublingual tablet, place the tablet under the tongue and allow it to dissolve completely. The tablet will dissolve in the saliva within seconds. Do not crush, chew, or swallow the tablet. Patients should be instructed not to eat or drink for 10 minutes after asenapine administration [1].

B) Sublingual route**1) Tablet**

- a) Store at controlled room temperature, 15 to 30 degrees C (59 to 86 degrees F) [2].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Sublingual route

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

a) Monotherapy

1) The recommended starting dose of asenapine as monotherapy for the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults is 10 mg sublingually twice daily. The dose can be decreased to 5 mg sublingually twice daily if there are adverse effects. The safety of doses above 10 mg twice daily has not been studied. There are no evidence addressing the duration of therapy, but it is recommended that patients who respond to treatment be continued on asenapine after the acute period and have risk/benefits of continued therapy reevaluated periodically [1].

b) Adjunctive Therapy

1) The recommended dose of asenapine when used as adjunctive therapy with either lithium or valproate for the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults is 5 mg sublingually twice daily. The dose can be increased to 10 mg sublingually twice daily based on clinical response. The safety of doses above 10 mg twice daily has not been studied. There are no evidence addressing the duration of therapy, but it is recommended that patients who respond to treatment be continued on asenapine after the acute period and have risk/benefits of continued therapy reevaluated periodically [1].

1.3.1.A.2] Schizophrenia, Acute treatment

a) The recommended starting and target dose of asenapine for the acute treatment of schizophrenia in adults is 5 mg sublingually twice daily. In controlled clinical trials, there was no added benefit with higher doses, but there was an increase in adverse reactions. The safety of doses above 10 mg twice daily has not been studied [1].

1.3.1.B] Switching from Other Antipsychotics

1) When switching from other antipsychotics, the period of overlapping therapies should be minimized [1].

1.3.2] Dosage in Renal Failure

A) No dose adjustments are required in patients with renal impairment [1].

1.3.3] Dosage in Hepatic Insufficiency

A) Asenapine is not recommended in patients with severe hepatic impairment (Child-Pugh C). No dose adjustments are required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment [1].

1.3.4] Dosage in Geriatric Patients

A) No dose adjustments are necessary based on age [1].

1.3.6] Dosage in Other Disease States

A) Gender

1) No dose adjustments are necessary based on gender [1].

B) Race

1) No dose adjustments are necessary based on race [1].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

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

2.0] Pharmacokinetics

Drug Concentration Levels

ADME

2.2] Drug Concentration Levels

A) Peak Concentration

1) Sublingual, single-dose, 5 mg: 4 ng/mL [2]

a) Following a single dose of sublingual asenapine 5 mg, the mean C_{max} was approximately 4 ng/mL [2].

B) Time to Peak Concentration

1) Sublingual: 0.5 to 1.5 hr [2]

a) Following sublingual administration of asenapine, peak plasma concentrations occurred within 0.5 to 1.5 hours with the mean T_{max} observed at 1 hour [2].

C) Steady State

1) Sublingual (multiple-dose): 3 days [2]

a) Steady state is achieved within 3 days with multiple-dose of twice-daily dosing of sublingual asenapine [2].

D) Area Under the Curve

1) Hepatic Impairment

a) In patients with severe [hepatic impairment](#) (Child-Pugh C), asenapine exposures after a single dose of 5 mg were 7-fold higher than in patients with normal hepatic function, therefore, it is not recommended in patients with severe [hepatic impairment](#). No dosage adjustments are required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) [hepatic impairment](#) [2].

2) Renal Impairment

a)) Exposure of asenapine after a single dose of 5 mg was similar in patients with normal renal function and in those with varying degrees of renal impairment, therefore, dosage adjustment is not required in renal impairment [2].

3)) Geriatric

a)) Exposures of asenapine in the elderly was up to 2-fold higher than the highest exposure in younger subjects. A decrease in clearance with increasing age was observed, implying a 30% higher exposure in elderly as compared to adult patients. Dosage adjustments are not routinely required on the basis of age [2].

2.3] ADME

2.3.1] Absorption

A)) Bioavailability

1)) Sublingual: 35% [2]

a)) Following sublingual administration, asenapine is rapidly absorbed. The absolute bioavailability after sublingual asenapine at 5 mg is 35%. A two-fold increase in dose from 5 mg to 10 mg results in less than linear (1.7 times) increases in both the AUC and C_{max}. The absolute bioavailability when swallowed is low (less than 2% with oral tablets) [2].

B)) Effects of Food

1)) Decreases drug exposure [2]

a)) During clinical trials, consumption of food immediately prior to sublingual administration decreased asenapine exposure by 20%, and 10% if food is consumed 4 hours after sublingual administration. Intake of water 2 to 5 minutes after sublingual administration also decreased exposure of the drug by 19% and 10%, respectively, therefore, take as directed per manufacture's recommendation and wait for 10 minutes before eating or drinking [2].

2.3.2] Distribution

A)) Distribution Sites

1)) Protein Binding

a)) Plasma proteins (including albumin and alpha 1-acid glycoprotein): 95% [2]

1)) Asenapine is highly bound to plasma proteins (95%), including albumin and alpha 1-acid glycoprotein [2].

2)) Tissues and Fluids

a)) Extravascular: extensive [2]

1) Asenapine is rapidly distributed and has a large Vd indicating extensive extravascular distribution [2].

B) Distribution Kinetics

1) Volume of Distribution

a) 20 to 25 L/kg [2]

1) Asenapine is rapidly distributed with a large volume of distribution, at approximately 20 to 25 L/kg [2]

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Hepatic: extensive via direct glucuronidation and oxidative metabolism [2]

a) The primary metabolic pathways of asenapine are direct glucuronidation by UGT1A4 and oxidative metabolism by predominantly CYP1A2. In vitro studies indicate that asenapine is a substrate for UGT1A4, CYP1A2 and to a lesser extent CYP3A4 and CYP2D6 [2].

b) Smoking, which induces CYP1A2, had no effect on the clearance of asenapine in a crossover study (n=24) in which healthy male patients were given a single 5 mg sublingual dose [2].

B) Metabolites

1) N(+)-glucuronide, N-desmethylenapine, and N-desmethylenapine N-carbamoyl glucuronide: inactive [2]

a) After administration of a single dose of asenapine, approximately 50% of the circulating species were identified in the plasma, with N(+)-glucuronide as the predominant species, N-desmethylenapine and N-desmethylenapine N-carbamoyl glucuronide as the other species, and unchanged asenapine in smaller amounts. The activity of asenapine is primarily due to the parent drug [2].

2.3.4] Excretion

A) Kidney

1) Renal Excretion (%)

a) 50% [2]

1) Approximately 90% of the dose was recovered after a single dose administration of asenapine, about 50% of which was recovered in the urine [2].

B) Feces

1) 40% [2]

a) Approximately 90% of the dose was recovered after a single dose administration of asenapine, about 40% of which was recovered in the feces [2].

C) Total Body Clearance

1) 52 L/hr (IV) Hepatic: extensive via direct glucuronidation and oxidative metabolism [2]

a) Asenapine clearance after intravenous administration is high at 52 L/hr, suggesting that hepatic clearance is influenced mostly by changes in liver blood flow instead of intrinsic clearance such as metabolizing enzymatic activity [2].

2.3.5] Elimination Half-life

A) Parent Compound

1) 24 hr [2]

a) The terminal half-life of asenapine after an initial more rapid distribution phase is about 24 hours [2].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.0.A] Black Box WARNING

Sublingual (Tablet)

Use of antipsychotic drugs increases the risk of death in elderly patients with dementia-related psychosis. Asenapine is not approved for treatment of patients with dementia-related psychosis [6].

3.1] Contraindications

A) hypersensitivity to the product [6]

3.2] Precautions

A) Black Box Warning:

B) -- use in elderly patients with dementia-related [psychosis](#) increases fatality risk (unapproved use), usually of cardiovascular (eg, sudden death, [heart failure](#)) or infectious causes (eg, [pneumonia](#)) [6]

C) Cardiovascular:

D) -- QT-interval prolongation or [Torsade de Pointes](#) may occur; avoid use in patients with a history of [cardiac arrhythmia](#), (including bradycardia), hypokalemia or hypomagnesemia, or congenital QT-interval prolongation [6]

E) -- orthostatic hypotension, especially early in treatment, has been reported, with increased risk in elderly patients and patients with [cardiovascular disease](#), [cerebrovascular disease](#), or predisposition to hypotension; monitoring and dose reduction may be warranted [6]

F) -- increased risk of cardiovascular effects with metabolic changes that occur with atypical antipsychotics (ie, [hyperglycemia](#), [dyslipidemia](#), weight gain) [6]

G) Endocrine Metabolic:

H) -- extreme [hyperglycemia](#) has been reported, which has progressed to [ketoacidosis](#), coma, and death; monitoring recommended [6]

I) -- patients with [diabetes mellitus](#) or with risk factors for [diabetes mellitus](#) (eg, [obesity](#), family history) at increased risk for severe [hyperglycemia](#); monitoring recommended [6]

J) -- avoid use in patients with hypokalemia or hypomagnesemia due to increased risk of QT-interval prolongation or [torsade de pointes](#) [6]

K) -- conditions that may contribute to elevated body temperature (eg, strenuous exercise, extreme heat exposure, dehydration, concomitant anticholinergic medications) may disrupt body temperature regulation [6]

L) -- [hyperprolactinemia](#) may occur and progress to decreased bone density (when associated with [hypogonadism](#)), [galactorrhea](#), [amenorrhea](#), [gynecomastia](#), and impotence [6]

M) -- [dyslipidemia](#) has occurred with atypical antipsychotic treatment [6]

N) -- weight gain has been reported; monitoring recommended [6]

O) Gastrointestinal:

P) -- not recommended for patients at risk for [aspiration pneumonia](#), as [esophageal dysmotility](#) and aspiration may occur [6]

Q) Hematologic:

R) -- [agranulocytosis](#), [leukopenia](#), and [neutropenia](#) have been reported; risk factors include preexisting low WBC and history of drug-induced [leukopenia](#) or [neutropenia](#); monitoring recommended; treatment interruption or withdrawal may be required [6]

S) Hepatic:

T) -- not recommended for patients with severe [hepatic impairment](#) (Child-Pugh C) [6]

U) Immunologic:

V) -- [hypersensitivity reactions](#) (eg, [anaphylaxis](#), [angioedema](#), hypotension, [tachycardia](#), swollen tongue, dyspnea, wheezing, and rash) have been reported [6]

W) Neurologic:

X) -- cerebrovascular adverse events ([stroke](#), [transient ischemic attack](#)), including fatalities, have been reported in elderly patients with dementia-related [psychosis](#) (unapproved use) and treated with atypical antipsychotics [6]

Y) -- potentially fatal [neuroleptic malignant syndrome](#) has been reported; drug discontinuation recommended and careful monitoring required with rechallenge [6]

Z) -- potentially irreversible [tardive dyskinesia](#) may occur, with increased risk with long-term therapy or higher cumulative doses; consider discontinuation if condition occurs [6]

AA) -- seizure has been reported; use with caution in patients with a history of seizure disorder or with conditions that may lower seizure threshold (eg, [Alzheimer dementia](#)) [6]

AB) -- syncope, especially early in treatment, has been reported, with increased risk in elderly patients and patients with [cardiovascular disease](#), [cerebrovascular disease](#), or predisposition to hypotension; monitoring and dose reduction may be warranted [6]

AC) -- increased risk of cerebrovascular effects with metabolic changes that occur with atypical antipsychotics (ie, [hyperglycemia](#), [dyslipidemia](#), weight gain) [6]

AD) Psychiatric:

AE) -- monitor for suicidality [6]

AF) Other:

AG) -- elderly patients (especially women) at increased risk of [tardive dyskinesia](#); consider discontinuation if condition occurs [6]

AH) -- carefully monitor patients aged 65 years and older for poor tolerance [6]

AI) Concomitant Use:

AJ]) -- avoid concomitant use with other drugs known to prolong QTc, including class 1A antiarrhythmics (eg, [quinidine](#), [procainamide](#)) or class 3 antiarrhythmics (eg, [amiodarone](#), [sotalol](#)), antipsychotic medications (eg, [ziprasidone](#), [chlorpromazine](#), [thioridazine](#)), and antibiotics (eg, [gatifloxacin](#), [moxifloxacin](#)) [6]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Orthostatic hypotension

1]) Orthostatic hypotension and syncope has occurred in some patients on asenapine therapy, especially at initiation of asenapine. Caution should be used for comorbidities including [cardiovascular disease](#) (history of [myocardial infarction](#) or [ischemic heart disease](#), [heart failure](#), or condition abnormalities), [cerebrovascular disease](#), conditions which would predispose patients to hypotension (dehydration, [hypovolemia](#), and treatment with antihypertensive medications), and advance age. Monitoring recommended [2]

3.3.1.B] Prolonged QT interval

1]) Asenapine was associated with increases of 2 to 5 msec in the QTc interval when compared to placebo in a dedicated QT study. Clinically stable adult patients with [schizophrenia](#) (n=151) were given asenapine 5 mg, 10 mg, 15 mg, and 20 mg twice daily, and placebo. Electrocardiographic assessments throughout the dosing interval at baseline and steady state indicated none of the patients had an increase in QTc of greater than or equal to 60 msec from baseline and none experienced a QTc of 500 msec or greater [2].

2]) Adult patients with [schizophrenia](#) or bipolar mania experienced post-baseline QT prolongation exceeding 500 msec at a comparable rate to placebo in clinical trials using 5 mg or 10 mg twice daily for 3 to 6 weeks. There were no reports of [Torsade de Pointes](#) or any adverse reactions associated with delayed ventricular repolarization [2].

3.3.1.C] Syncope

1]) Orthostatic hypotension and syncope has occurred in some patients on asenapine therapy, especially at initiation of asenapine. Caution should be used for comorbidities including [cardiovascular disease](#) (history of [myocardial infarction](#) or [ischemic heart disease](#), [heart failure](#), or condition abnormalities), [cerebrovascular disease](#), conditions which would predispose patients to hypotension (dehydration, [hypovolemia](#), and treatment with antihypertensive medications), and advance age. Monitoring recommended [2]

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Weight increased

1]) Incidence: 3% to 5% [2]

2]) In four 6-week trials in adult patients with [schizophrenia](#), an increase in weight was reported in 3% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with less than 1% of patients who received placebo (n=378) [2].

3]) In two 3-week trials in adult patients with bipolar mania, an increase in weight was reported in 5% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with less than 1% of patients who received placebo (n=203). [2].

3.3.4] Gastrointestinal Effects

3.3.4.A] Application site reaction

1) Application site reactions, including oral ulcers, blisters, peeling/sloughing, and inflammation, primarily in the sublingual area have been reported during postmarketing surveillance of asenapine [7].

3.3.4.B] Excessive salivation

1) Incidence: 2% [7]

2) In four 6-week trials in adult patients with schizophrenia, salivary hypersecretion was reported in 2% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 0% of patients who received placebo (n=378) [7].

3.3.4.C] Increased appetite

1) Incidence: 2% to 4% [7]

2) In four 6-week trials in adult patients with schizophrenia, increased appetite was reported in 2% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with less than 1% of patients who received placebo (n=378) [7].

3) In two 3-week trials in adult patients with bipolar mania, increased appetite was reported in 4% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 1% of patients who received placebo (n=203). [7].

3.3.4.D] Indigestion

1) Incidence: 4% [7]

2) In two 3-week trials in adult patients with bipolar mania, dyspepsia was reported in 4% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 2% of patients who received placebo (n=203). [7].

3.3.4.E] Oral hypoesthesia

1) Incidence: 4% to 5% [7]

2) In four 6-week trials in adult patients with schizophrenia, oral hypoesthesia was reported in 5% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 1% of patients who received placebo (n=378) [7].

3) In two 3-week trials in adult patients with bipolar mania, oral hypoesthesia was reported in 4% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with less than 1% of patients who received placebo (n=203). [7].

3.3.4.F] Stomach ache

1) Incidence: 2% [7]

2) In four 6-week trials in adult patients with schizophrenia, stomach discomfort was reported in 2% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 1% of patients who received placebo (n=378) [7].

3.3.4.G] Taste sense altered

1) Incidence: 3% [7]

2) In two 3-week trials in adult patients with bipolar mania, dysgeusia was reported in 3% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with less than 1% of patients who received placebo (n=203). [7].

3.3.4.H] Toothache

1) Incidence: 3% [7]

2) In two 3-week trials in adult patients with bipolar mania, toothache was reported in 3% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 2% of patients who received placebo (n=203). [7].

3.3.4.I] Xerostomia

1) Incidence: 2% to 3% [7]

2) In four 6-week trials in adult patients with [schizophrenia](#), dry mouth was reported in 2% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 1% of patients who received placebo (n=378) [7].

3) In two 3-week trials in adult patients with bipolar mania, dry mouth was reported in 3% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 1% of patients who received placebo (n=203). [7].

3.3.5] Hematologic Effects**3.3.5.A] Agranulocytosis**

1) [Agranulocytosis](#), including fatal cases, has been reported with other agents in this class [2].

3.3.5.B] Leukopenia

1) [Leukopenia](#) has been temporally related to antipsychotic drugs, including asenapine, in clinical trials [2].

3.3.5.C] Neutropenia

1) [Neutropenia](#) has been temporally related to antipsychotic drugs, including asenapine, in clinical trials [2].

3.3.7] Immunologic Effects**3.3.7.A] Hypersensitivity reaction**

1) [Hypersensitivity reactions](#) (eg, [anaphylaxis](#), [angioedema](#), hypotension, [tachycardia](#), swollen tongue, dyspnea, wheezing and rash) have been reported in patients who received asenapine. Reactions occurred after the first dose in several cases [8].

2) Between August 2009 and September 2010, 52 cases of [type I hypersensitivity reactions](#) associated with asenapine use, including [anaphylaxis](#) and [angioedema](#), have been reported to the United States Food and Drug Administration. Of the 52 cases, 8 reported [hypersensitivity reactions](#) after the first dose of asenapine and some cases reported experiencing more than one reaction. Fifteen of the 52 cases reported a resolution of symptoms upon discontinuation of asenapine, however, a reintroduction of asenapine resulted in the reemergence of symptoms in 2 patients. Hospitalization or emergency room visits were reported in 19 of the 52 cases and 7 required therapeutic intervention. [Type I hypersensitivity reactions](#) including [anaphylaxis](#), [angioedema](#), hypotension, [tachycardia](#), swollen tongue, dyspnea, wheezing and rash, are usually the result of prior exposure to asenapine, although this is not true in all cases [9].

3.3.8] Musculoskeletal Effects

3.3.8.A] Arthralgia

1) Incidence: 3% [2]

2) In two 3-week trials in adult patients with bipolar mania, arthralgia was reported in 3% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 1% of patients who received placebo (n=203). [2].

3.3.8.B] Pain, Extremity

1) Incidence: 2% [2]

2) In two 3-week trials in adult patients with bipolar mania, pain in an extremity was reported in 2% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with less than 1% of patients who received placebo (n=203). [2].

3.3.9] Neurologic Effects**3.3.9.A] Akathisia**

1) Incidence: 4% to 6% [2]

2) In four 6-week trials in adult patients with [schizophrenia](#), [akathisia](#) and hyperkinesia were reported in 6% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 3% of patients who received placebo (n=378) [2].

3) In two 3-week trials in adult patients with bipolar mania, [akathisia](#) was reported in 4% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 2% of patients who received placebo (n=203) [2].

3.3.9.B] Dizziness

1) Incidence: 5% to 11% [2]

2) In four 6-week trials in adult patients with [schizophrenia](#), dizziness was reported in 5% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 4% of patients who received placebo (n=378) [2].

3) In two 3-week trials in adult patients with bipolar mania, dizziness was reported in 11% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 3% of patients who received placebo (n=203). [2].

3.3.9.C] Extrapyramidal disease

1) Incidence: 7% to 10% [2]

2) In four 6-week trials in adult patients with [schizophrenia](#), extrapyramidal symptoms were reported in 10% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 7% of patients who received placebo (n=378). The extrapyramidal symptoms included [dystonia](#), oculogyration, [dyskinesia](#), [tardive dyskinesia](#), muscle rigidity, [parkinsonism](#), tremor, and [extrapyramidal disorder](#) (excluding [akathisia](#)) [2].

3) In two 3-week trials in adult patients with bipolar mania, extrapyramidal symptoms were reported in 7% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 2% of patients who received placebo (n=203). The extrapyramidal symptoms included [dystonia](#), [blepharospasm](#), torticollis, [dyskinesia](#), [tardive dyskinesia](#), muscle rigidity, [parkinsonism](#), gait disturbance, masked facies, and tremor (excluding [akathisia](#)) [2].

3.3.9.D] Headache

1) Incidence: 12% [2]

2) In two 3-week trials in adult patients with bipolar mania, headache was reported in 12% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 11% of patients who received placebo (n=203). [2].

3.3.9.E] Insomnia

1) Incidence: 6% to 15% [2]

2) In four 6-week trials in adult patients with [schizophrenia](#), insomnia was reported in 15% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 13% of patients who received placebo (n=378) [2].

3) In two 3-week trials in adult patients with bipolar mania, insomnia was reported in 6% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 5% of patients who received placebo (n=203). [2].

3.3.9.F] Somnolence

1) Incidence: 13% to 24% [2]

2) In four 6-week trials in adult patients with [schizophrenia](#), somnolence was reported in 13% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with 7% of patients who received placebo (n=378) [2].

3) In two 3-week trials in adult patients with bipolar mania, somnolence was reported in 24% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 6% of patients who received placebo (n=203) [2].

3.3.12] Psychiatric Effects

3.3.12.A] Anxiety

1) Incidence: 4% [2]

2) In two 3-week trials in adult patients with bipolar mania, anxiety was reported in 4% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 2% of patients who received placebo (n=203). [2].

3.3.12.B] Depression

1) Incidence: 2% [2]

2) In two 3-week trials in adult patients with bipolar mania, depression was reported in 2% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 1% of patients who received placebo (n=203). [2].

3.3.12.C] Irritability

1) Incidence: 2% [2]

2) In four 6-week trials in adult patients with [schizophrenia](#), irritability was reported in 2% of patients who received asenapine 5 mg or 10 mg twice daily (n=572) compared with less than 1% of patients who received placebo (n=378) [2].

3.3.16] Other

3.3.16.A] [Angioedema](#)

1J) Between August 2009 and September 2010, 52 cases of [type I hypersensitivity reactions](#), including [angioedema](#), associated with asenapine use have been reported to the United States Food and Drug Administration. Of the 52 cases, 8 reported [hypersensitivity reactions](#) after the first dose of asenapine and some cases reported experiencing more than one reaction. Fifteen of the 52 cases reported a resolution of symptoms upon discontinuation of asenapine, however, a reintroduction of asenapine resulted in the reemergence of symptoms in 2 patients. Hospitalization or emergency room visits were reported in 19 of the 52 cases and 7 required therapeutic intervention. [Type I hypersensitivity reactions](#) including [anaphylaxis](#), [angioedema](#), hypotension, [tachycardia](#), swollen tongue, dyspnea, wheezing and rash, are usually the result of prior exposure to asenapine, although this is not true in all cases [9].

3.3.16.BJ Death

1J) Elderly patients with dementia-related [psychosis](#) treated with atypical antipsychotics had a 1.6 to 1.7 times greater risk of death compared with placebo (4.5% vs 2.6%) in 17 placebo-controlled clinical studies (modal duration 10 weeks). The cause of death varied, but most were associated with cardiovascular events including [heart failure](#), or infectious events including [pneumonia](#). Observational studies suggest treatment with conventional antipsychotic drugs may also increase mortality. The extent to which this observed increase in mortality is associated with [antipsychotic drug therapy](#) is not clear. Asenapine is not approved for the treatment of dementia-related [psychosis](#) [10].

2J) 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 1.7); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both 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 [11].

3J) 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 (age 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 compared with atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were

compared with [risperidone](#), the mortality ratio associated with [haloperidol](#) was 2.14 (95% CI, 1.86 to 2.45) and [loxapine](#) was 1.29 (95% CI, 1.19 to 1.4), while there was no difference associated with [olanzapine](#). The increased mortality risk for conventional compared with 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 [12].

3.3.16.C] Fatigue

1) Incidence: 4% [2]

2) In two 3-week trials in adult patients with bipolar mania, fatigue was reported in 4% of patients who received asenapine 5 mg or 10 mg twice daily (n=379) compared with 2% of patients who received placebo (n=203). [2].

3.3.16.D] Neuroleptic malignant syndrome

1) Potentially fatal [neuroleptic malignant syndrome](#) has been reported in association with antipsychotic drugs, including asenapine [2].

3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

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

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) There are no adequate and well-controlled studies of asenapine use during pregnancy; however, third-trimester antipsychotic drug exposure has been associated with extrapyramidal and/or withdrawal symptoms in neonates. In animal studies, asenapine increased post-implantation loss and decreased pup weight and survival at doses similar to or less than recommended clinical doses. Therefore, asenapine should be given during pregnancy only if the potential benefit to the mother outweighs the potential [risk to the fetus](#) [126].

4) Literature Reports

a) Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care [126].

b) There are no adequate and well-controlled studies of asenapine use in pregnant women. In animal studies, there was no evidence of [teratogenicity](#) when rats and rabbits were given IV doses

up to 1.5 mg/kg (0.7 times the maximum recommended human dose (MRHD) of 10 mg twice daily given sublingually on a mg/m² basis) and 0.44 mg/kg (0.4 times the MRHD), respectively. In the rabbit study, the asenapine AUC at the highest dose tested was 2 times that in humans receiving the MRHD. Increases in post-implantation loss and early pup deaths were seen at all doses, and decreases in subsequent pup survival and weight gain were seen at the 2 higher doses when rats were treated from day 6 of gestation through day 21 postpartum with IV doses of asenapine of 0.3, 0.9, and 1.5 mg/kg/day (0.15, 0.4, and 0.7 times the MRHD). In a cross-fostering study, the decreases in pup survival were shown to be largely due to prenatal drug effects. Increases in post-implantation loss and decreases in pup weight and survival were also reported in pregnant rats given oral asenapine [126].

B) Breastfeeding

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

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

2) Clinical Management

a) It is not known whether asenapine or its metabolites are excreted in human milk. In animal lactation studies, asenapine was excreted in milk of rats. Because many drugs are excreted in human milk, it is recommended that mothers receiving asenapine should not breastfeed. If asenapine use is required, caution should be exercised when the drug is given to the nursing mother [126].

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] Acecainide

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

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.B] Ajmaline

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class IA antiarrhythmic drugs known for QT prolongation (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine with class IA antiarrhythmics (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) 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](#) [2]. 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.C] [Alfuzosin](#)

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

2) Summary: Both [alfuzosin](#) and asenapine have been associated with QT prolongation [14] [69]. Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of [alfuzosin](#) with asenapine should be avoided [14]. If coadministration is required, monitor closely for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [alfuzosin](#) with asenapine should be avoided due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [14]. However, if concurrent therapy is required, monitor ECG closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) In a postmarketing study that evaluated the effect of concomitant administration of [alfuzosin](#) with another QT interval-prolonging drug of similar effect size, the observed QT interval prolongation was greater than that seen with either drug alone, but was not more than additive. The corrected (Fridericia) QT interval (QTcF) increased by 5.9 milliseconds (upper bound of 95% confidence interval (CI), 9.4 milliseconds). The QTcF increase observed with [moxifloxacin](#) 400 mg (positive control) was 10.2 milliseconds (upper bound 95% CI, 13.8 milliseconds). The mean placebo-subtracted QTcF increase following administration of [alfuzosin](#) 10 mg alone was 1.9 milliseconds (upper bound 95% CI, 5.5 milliseconds) [69].

b) In an electrocardiographic assessment in clinically stable patients with [schizophrenia](#) (n=151), QT interval increased 2 to 5 milliseconds with asenapine compared with placebo at doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily. No patients experienced QT interval increases of 60 milliseconds or more from baseline or [torsade de pointes](#). Reports of QT intervals of 500 milliseconds or more occurred at rates comparable to placebo [14].

3.5.1.D] [Amifampridine](#)

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

2) Summary: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#) [84].

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amifampridine with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of [ventricular arrhythmias](#) [84].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.E] [Amiodarone](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.F] [Amisulpride](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Coadministration of asenapine with other antipsychotic drugs associated with QT-interval prolongation (eg, amisulpride, [haloperidol](#), [risperidone](#)) should be avoided as additive QT prolongation may occur [2]. If concurrent use of asenapine with another antipsychotic known to prolong the QT interval is required, monitor for QT-interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine with other drugs that prolong the QT interval, such as antipsychotic agents (eg, amisulpride, [haloperidol](#), [risperidone](#)), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. If concurrent therapy is required, monitor patient closely for QT-interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.G] [Amitriptyline](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using [amitriptyline](#) and asenapine concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Additionally asenapine is a weak CYP2D6 inhibitor and [14] [amitriptyline](#) is a CYP2D6 substrate [94].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: Avoid using [amitriptyline](#) and asenapine concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [14].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.H] [Amoxapine](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Both asenapine and [amoxapine](#) may prolong the QT interval. Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of asenapine with drug that prolong the QT interval, such as [amoxapine](#), should be avoided [14]. However, if concurrent therapy is required, monitor closely for prolongation of the QT interval.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [amoxapine](#) with asenapine should be avoided due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [14]. However, if concurrent therapy is required, monitor closely for prolongation of the QT interval.
- 7) Probable Mechanism: additive effects on QT interval prolongation
- 8) Literature Reports

a) In a electrocardiographic assessment in clinically stable patients with [schizophrenia](#) (n=151), QT interval increased 2 to 5 milliseconds with asenapine compared with placebo at doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily. No patients experienced QT interval increases of 60 milliseconds or more from baseline or [torsade de pointes](#). Reports of QT intervals of 500 milliseconds or more occurred at rates comparable to placebo [14].

3.5.1.I] [Apomorphine](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [apomorphine](#) and asenapine, both drugs that prolong the QT interval, may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [31] [14]; therefore, coadministration is not recommended [14]. If concurrent administration is required, caution is advised [31]. Monitor closely for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [apomorphine](#) and asenapine, both drugs that prolong the QT interval, may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [31] [14]; therefore, coadministration is not recommended [14]. If concurrent administration is required, caution is advised [31]. Monitor closely for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.J] [Aripiprazole](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: [Aripiprazole](#) has been associated with QTc interval prolongation [122], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: [Aripiprazole](#) has been associated with QTc interval prolongation [122], and coadministration with another drug known to prolong the QT interval should be undertaken with caution because of risk for additive effects on the QT interval that can lead to serious cardiac adverse effects, including [torsade de pointes](#).
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.K] Arsenic Trioxide

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), concomitant use of asenapine with [arsenic trioxide](#) should be avoided [2] [24]. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and [arsenic trioxide](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2] [23]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval
- 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 [24].

3.5.1.L] Artemether

- 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, including asenapine, should be avoided. If concomitant administration with artemether/lumefantrine and asenapine is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy due to the long half-life of lumefantrine (3 to 6 days) [101].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid coadministration of artemether/lumefantrine with drugs that prolong the QT interval, including asenapine, due to the potential for additive effects on QT-interval prolongation. If concomitant administration of artemether/lumefantrine and asenapine is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy due to the long half-life of lumefantrine (3 to 6 days) [101].
- 7) Probable Mechanism: additive effects on QT-interval prolongation

3.5.1.M] Astemizole

- 1J) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2J) Summary: Both asenapine and [astemizole](#) may prolong QT interval. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and [astemizole](#) [2]. However, if concurrent therapy is required, monitor carefully for QT interval prolongation.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of asenapine and [astemizole](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7J) Probable Mechanism: additive effects on QT interval

3.5.1.N] Azimilide

- 1J) Interaction Effect: an increased risk of QT interval prolongation
- 2J) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
- 7J) Probable Mechanism: additive effects on the QT interval

3.5.1.O] Azithromycin

- 1J) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2J) Summary: Both asenapine and [azithromycin](#) may prolong QT interval [2] [36]. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and drugs that may prolong the QT interval, such as [azithromycin](#) [2]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of asenapine and [azithromycin](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2] [36]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7J) Probable Mechanism: additive effects on QT interval

3.5.1.P] Bedaquiline

- 1) Interaction Effect: increased risk of QT prolongation
- 2) Summary: Bedaquiline is associated with QT-interval prolongation. Concomitant administration of bedaquiline with other drugs that prolong the QT interval, including fluoroquinolones, macrolide antibacterial drugs, and the antimycobacterial drug, [clofazimine](#), may have additive prolonging effects on the QT interval. Close monitoring of baseline and on-treatment ECGs are recommended when bedaquiline is coadministered with other QT-prolonging agents [60].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of bedaquiline and other QT-prolonging drugs may result in additive prolongation effects on the QT interval. Baseline and on-treatment ECGs should be monitored closely when bedaquiline is coadministered with other QT-prolonging agents, including fluoroquinolones, macrolide antibacterial drugs, and the antimycobacterial drug, [clofazimine](#) [60].
- 7) Probable Mechanism: additive QT-interval prolongation
- 8) Literature Reports

a) The mean increase in QTc interval at week 24 was greater in patients who received concomitant bedaquiline and [clofazimine](#), compared with patients who received bedaquiline without [clofazimine](#) (mean change from reference, 31.9 msec vs 12.3 msec, respectively) in an open-label, noncomparative study in previously treated patients with multidrug-resistant pulmonary Mycobacterium [tuberculosis](#) [60].

3.5.1.Q] Bretylium

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.R] Buserelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs [113] [114] [115]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur [113] [114] [115].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.S] Chloroquine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of asenapine with drugs that prolong the QT interval, such as [chloroquine](#), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and [chloroquine](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.T] Chlorpromazine

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Asenapine and [chlorpromazine](#) both may cause QT interval prolongation [14] [56]. The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [chlorpromazine](#) [56], should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events [14]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [chlorpromazine](#) [56], should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events [14]. If coadministration is required, monitoring for QT interval prolongation may be warranted.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.U] Ciprofloxacin

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of [ciprofloxacin](#) and other QT prolonging drugs, such as asenapine, may increase the risk of QT interval prolongation and should be avoided [14]. Geriatric patients may be particularly sensitive to QT prolongation [45]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

- 6) Clinical Management: Coadministration of asenapine and [ciprofloxacin](#), both drugs that prolong the QT interval, may increase the potential for serious cardiovascular effects and should be avoided [14]. Geriatric patients may be particularly sensitive to QT prolongation [45]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.V] [Cisapride](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: [Cisapride](#) prolongs the QT interval. An additive effect on the QT interval can be expected when [cisapride](#) is coadministered with a drug that prolongs the QT interval, such as asenapine [2]. Therefore the concurrent administration of [cisapride](#) and asenapine is contraindicated [16].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [cisapride](#) and a drug that prolongs the QT interval, such as asenapine, is contraindicated [16].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.W] [Citalopram](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of asenapine and [citalopram](#) is not recommended as both agents have been associated with QT prolongation [105] [8]. Although this interaction has not been evaluated, the concomitant use of asenapine with [citalopram](#) may increase the risk of QT interval prolongation and [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [105].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the coadministration of asenapine and [citalopram](#) as both agents are known to increase the QT interval and concurrent use may increase the risk of cardiac adverse events [105] [8], including [torsade de pointes](#). If coadministration is required, monitor for ECG changes. Do not exceed [citalopram](#) doses of 40 mg/day and discontinue [citalopram](#) in patients who have persistent QTc measurements greater than 500 milliseconds [105].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.X] [Clarithromycin](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: Both asenapine and [clarithromycin](#) may prolong the QT interval. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and [clarithromycin](#) [2] [46]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. [Clarithromycin](#), like other macrolide antibiotics, has been associated with QT prolongation, including [torsade de pointes](#) [46]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of asenapine with [clarithromycin](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.Y] [Clomipramine](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Avoid using asenapine and [clomiPRAMINE](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events. Additionally, asenapine is a weak CYP2D6 inhibitor and [14] [clomiPRAMINE](#) is a CYP2D6 substrate. Monitoring plasma levels of [clomiPRAMINE](#) may be warranted with used in combination with CYP2D6 inhibitors [17].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid using asenapine and [clomiPRAMINE](#) concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular events [14].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.Z] [Clonidine](#)

- 1) Interaction Effect: induction or exacerbation of orthostatic regulation disturbances
- 2) Summary: Coadministration of [clonidine](#) with neuroleptics, such as asenapine [14], may result in orthostatic regulation disturbance induction or exacerbation [64] [65] and should be approached with caution.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [clonidine](#) and neuroleptics, such as asenapine [14], may induce or exacerbate orthostatic regulation disturbances (eg, dizziness, fatigue, orthostatic hypotension) [64] [65] and should be approached with caution.
- 7) Probable Mechanism: unknown

3.5.1.AA] [Clozapine](#)

- 1) Interaction Effect: increased risk of QT prolongation
- 2) Summary: [Clozapine](#) is associated with QT-interval prolongation. Concomitant administration of [clozapine](#) with other drugs that prolong the QT interval may result in additive prolongation effects on the QT interval and increase the risk of serious cardiac events, including [ventricular arrhythmias](#) and [torsade de pointes](#). If concomitant therapy is required, use caution and monitor the patient closely for QT-interval prolongation. Discontinue [clozapine](#) if the corrected QT interval exceeds 500 milliseconds. Cardiac evaluation and treatment discontinuation are warranted if the patient develops symptoms of [torsade de pointes](#) or other [arrhythmias](#) [79].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of [clozapine](#) and QT-prolonging drugs may result in additive prolongation effects on the QT interval. If concomitant therapy is required, use caution and monitor the patient closely for QT-interval prolongation. Discontinue [clozapine](#) if the corrected QT

interval exceeds 500 milliseconds. Cardiac evaluation and treatment discontinuation are warranted if the patient develops symptoms of [torsade de pointes](#) or other [arrhythmias](#) [79].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.AB| Crizotinib

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

2J) Summary: QT-interval prolongation has occurred during crizotinib therapy. Risk of additive QT-interval prolongation increases during coadministration with other drugs associated with QT prolongation. If concomitant use is clinically indicated, use caution and consider periodic ECG and [electrolyte monitoring](#) during therapy [44]. Dose reduction of crizotinib may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution in coadministering crizotinib with a drug known to prolong the QT interval, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events. If concomitant use is clinically indicated, consider periodic ECG and [electrolyte monitoring](#) during therapy [44]. Dose reduction of crizotinib may be warranted.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.AC| Cyclobenzaprine

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

2J) Summary: [Cyclobenzaprine](#) is structurally related to tricyclic antidepressants, which are known to prolong the QT interval [19]. In a case report, the combination of [fluoxetine](#) and [cyclobenzaprine](#) was suspected to have caused asymptomatic QT-interval prolongation in a female patient, which progressed to [torsade de pointes](#) and [ventricular fibrillation](#) after preoperative administration of [droperidol](#), a drug known to prolong the QT interval and cause [torsade de pointes](#) [20]. Due to the potential for additive effects on QT-interval prolongation, the concomitant use of [cyclobenzaprine](#) with drugs that prolong the QT interval is not recommended. However, if concurrent use is required, monitor the patient for [cardiac arrhythmias](#) and QT-interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: [Cyclobenzaprine](#) is structurally related to tricyclic antidepressants, which are known to prolong the QT interval [19]. Coadministration of [cyclobenzaprine](#) 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 use is required, monitor the patient for [cardiac arrhythmias](#) and QT-interval prolongation.

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

8J) Literature Reports

aJ) A 59-year-old woman developed [torsade de pointes](#), progressing to [ventricular fibrillation](#) and [cardiac arrest](#), after receiving [droperidol](#) during elective Achilles [tendon surgery](#) the day after discontinuing [cyclobenzaprine](#). Five days prior to the surgery, her QTc was prolonged at 497 milliseconds (msec); magnesium and potassium were within normal limits. Her home medication regimen, which was discontinued the day prior to surgery, included [cyclobenzaprine](#) 10 mg/day and [fluoxetine](#) 30 mg/day, as well as [amlodipine](#), [diclofenac](#), and [triamterene/hydrochlorothiazide](#). She was premedicated 45 minutes prior to surgery with [droperidol](#) 0.625 mg IV and [metoclopramide](#) 10 mg IV. Approximately 1 hour and 45 minutes after the surgery had started, the patient developed [ventricular tachycardia](#) consistent with [torsade de pointes](#) which progressed into

ventricular fibrillation and cardiac arrest. Immediately following cardioversion, the patient's QTc was 500 msec with no evidence of ischemic injury. On postoperative day 1, her QT interval had normalized to 440 msec, which was below her baseline value, and an ECG showed normal sinus rhythm. The patient had no known history of cardiac disease or evidence of risk factors associated with torsade de pointes or other dysrhythmias. All preadmission medications were restarted at discharge, with the exception of cyclobenzaprine [20].

3.5.1.AD] Dabrafenib

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Dabrafenib, as a single agent, has potential to prolong the QT interval; therefore, concomitant use with other drugs that can prolong the QT interval may cause additive effects on the QT interval [54]. Therefore, caution should be exercised with concomitant use [55] and consider assessment and periodic monitoring for ventricular arrhythmia.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of dabrafenib with other drugs that cause QT-interval prolongation may result in additive effects on the QT interval [54]. Exercise caution with concomitant use [55] and consider assessment and periodic monitoring for ventricular arrhythmia.
- 7) Probable Mechanism: additive QT prolongation

3.5.1.AE] Dasatinib

- 1) Interaction Effect: increased risk of QT interval prolongation and torsade de pointes
- 2) Summary: Both asenapine [2] and dasatinib [83] have been associated with QT interval prolongation. Due to the potential for additive effects on the QT interval and risk of torsade de pointes, the concomitant use of asenapine and dasatinib should be avoided [2]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. If concomitant use is required, close monitoring of cardiac function is warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and dasatinib may result in additive effects on the QT interval and an increased risk of torsade de pointes, and therefore should be avoided [2]. If concurrent therapy is required, monitor cardiac function closely.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.AF] Delamanid

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg more than once a month) during the full course of delamanid therapy [90].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Delamanid is a QT-interval-prolonging drug. Treatment initiation is not recommended in patients on other QT-interval-prolonging agents due to increased risk of the additive QT-interval prolongation effect. If the concurrent use cannot be avoided, an ECG should be obtained baseline and frequently (eg more than once a month) during the full course of delamanid therapy [90].

7) Probable Mechanism: additive QT- interval prolongation

3.5.1.AG] Desipramine

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

2) Summary: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [desipramine](#) (particularly at high doses) [124], should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events [14]. If concomitant use is required, close monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [desipramine](#) (especially at high doses) [124], should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events [14]. If concurrent therapy is required, monitor cardiac function closely.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AH] Deslorelin

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs [113] [114] [115]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur [113] [114] [115].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AI] Disopyramide

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class IA antiarrhythmic drugs known for QT prolongation (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) should be avoided . In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine with class IA antiarrhythmics (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) 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](#) [2]. 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.AJ] [Dofetilide](#)

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

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AK] [Dolasetron](#)

1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2) Summary: Both asenapine and [dolasetron](#) may prolong QT interval [86]. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and [dolasetron](#) [2]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc intervals increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and [dolasetron](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) For [dolasetron](#), QT prolongation appears to be associated with concentrations of hydrodolasetron. Following a single IV dose of 1.8 mg/kg to pediatric and adult [cancer](#) patients, the mean predicated increase (95% upper confidence bound) in QT intervals were 22.5 milliseconds (23.9 milliseconds) and 21.2 milliseconds (22.6 milliseconds). The mean maximum differences in QT from placebo after baseline-correction were 14.1 milliseconds (95% upper confidence bound, 16.1 milliseconds) and 36.6 milliseconds (95% upper confidence bound, 38.6 milliseconds) for 100 mg and 300 mg, respectively, of [dolasetron](#) IV in a controlled crossover study (n=80) with 14 measurements over 24 hours. [86]

3.5.1.AL] Domperidone

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Avoid coadministration of asenapine, a QT prolonging drug [14], and domperidone, a drug that has been associated with an increased risk of sudden cardiac death. In case control studies, an increased risk of sudden cardiac death was observed with the use of oral domperidone, particularly at doses greater than 30 mg/day and in patients older than 60 years of age. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [118].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of asenapine and domperidone as this may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death [14], particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. If coadministration is necessary, domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [118].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AM] Dronedaron

- 1) Interaction Effect: an increased risk of [torsade de pointes](#)
- 2) Summary: Due to the potential for additive effects on the QT interval prolongation and increased risk of [torsade de pointes](#), the concomitant use of dronedarone and asenapine is contraindicated [13].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of dronedarone and asenapine is contraindicated due to the potential for additive effects on the QT interval and an increased risk of [torsade de pointes](#) [13].
- 7) Probable Mechanism: additive effects on the QT interval prolongation

3.5.1.AN] Droperidol

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Both asenapine and [droperidol](#) have been associated with QT prolongation [2] [15]. [Droperidol](#) should not be administered with any drug known to have the potential to prolong the QT interval [15]. In an ECG study of 151 clinically stable patients, administration of asenapine in doses of 5, 10, 15, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc intervals increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. While concomitant use of asenapine and [droperidol](#) has not been specifically evaluated, the concomitant use of asenapine and [droperidol](#) should be avoided [15] [2]. If concomitant use cannot be avoided, extreme caution and [ECG monitoring](#) (prior to treatment and 2 to 3 hours after completing treatment) is recommended [15].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and [droperidol](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [14] [15]. If concomitant use cannot be avoided, extreme caution and [ECG monitoring](#) (prior to treatment and 2 to 3 hours after completing treatment) is recommended [15].

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

3.5.1.AO] Erythromycin

1J) Interaction Effect: an increased risk of QT interval prolongation and [torsade de pointes](#)

2J) Summary: Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), concomitant use of asenapine with [erythromycin](#) should be avoided. In an ECG study of 151 clinically stable patients, administration of asenapine in doses of 5, 10, 15, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc interval increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. [Erythromycin](#) use has been associated with QT prolongation and [ventricular arrhythmias](#), including [torsade de pointes](#) [85]. If concomitant use is required, the patient should be closely monitored for prolongation of the QT interval.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of asenapine with [erythromycin](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

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

3.5.1.AP] Escitalopram

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

2J) Summary: Escitalopram is a QT-interval-prolonging drug [59]. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Escitalopram is a QT-interval-prolonging drug [59]. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation.

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.AQ] Fentanyl

1J) Interaction Effect: increased risk of CNS depression

2J) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death [29]. Severe hypotension has been reported with coadministration of [fentanyl](#) and [midazolam](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [30]. Due to the risk of additive CNS effects, use caution, monitor patients closely, and reduce the dose of one or both when these agents are administered concomitantly [29].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents [29].

7J) Probable Mechanism: additive CNS depression

3.5.1.AR] Fingolimod

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

2J) Summary: Asenapine and fingolimod have been associated with an increased risk of QT interval prolongation [58] [14]. Initiating fingolimod therapy may decrease heart rate and prolong the QT interval. Drugs that prolong the QT interval, such as asenapine, may increase the risk of [torsade de pointes](#) in patients with bradycardia [58]. Therefore, concomitant use of asenapine and fingolimod should be avoided [14]. However, if concomitant use is clinically warranted, observe asenapine-treated patients with [continuous ECG monitoring](#) overnight in a medical facility when initiating fingolimod therapy [58].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant administration of asenapine and fingolimod as this may result in additive effects on the QT interval, and may increase the risk of serious cardiovascular effects including [torsade de pointes](#) [14]. If coadministration is necessary, observe asenapine-treated patients with [continuous ECG monitoring](#) overnight in a medical facility when initiating fingolimod therapy [58]

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

3.5.1.AS] Flecainide

1J) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2J) Summary: Both asenapine and [flecainide](#) may prolong QT interval. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and drugs that may prolong the QT interval, such as [flecainide](#) [2] [63]. However, if concurrent therapy is required, monitor carefully for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of asenapine and [flecainide](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2] [63]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.AT] Fluconazole

1J) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2J) Summary: Both asenapine and [fluconazole](#) may prolong QT interval. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and [fluconazole](#) [2] [67]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. Cases of QT interval prolongation and serious [arrhythmias](#), including [torsades de pointes](#), have been reported postmarketing with [fluconazole](#) use [67]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6)) Clinical Management: Concomitant use of asenapine and [fluconazole](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2] [67]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.AU] [Fluoxetine](#)

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

2)) Summary: [Fluoxetine](#) use is associated with reports of QT interval prolongation and [ventricular arrhythmia](#), included [torsade de pointes](#). Concomitant use of [fluoxetine](#) and QT-prolonging drugs may result in additive prolongation of the QT interval. Therefore, coadministration should be avoided [125]. If coadministration with [fluoxetine](#) is necessary, consider a baseline ECG and on-treatment monitoring.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Avoid the concomitant use of [fluoxetine](#) with other drugs known to prolong the QT interval [125]. If coadministration with [fluoxetine](#) is necessary, consider a baseline ECG and on-treatment monitoring.

7)) Probable Mechanism: additive QT-interval prolonging effects

3.5.1.AV] [Fluvoxamine](#)

1)) Interaction Effect: increased exposure to asenapine

2)) Summary: The C_{max} and AUC of asenapine increased by 13% and 29%, respectively, after a single 5-mg dose of asenapine in healthy volunteers administered [fluvoxamine](#) 25 mg twice daily for 8 days. Furthermore, greater increases in asenapine exposure would be likely with full therapeutic doses of [fluvoxamine](#). Concomitant use of asenapine and [fluvoxamine](#) should be used with caution [2].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Concomitant use of asenapine and [fluvoxamine](#) should be used with caution [2].

7)) Probable Mechanism: inhibition of CYP1A2-mediated asenapine metabolism

3.5.1.AW] [Formoterol](#)

1)) Interaction Effect: increased risk of [ventricular arrhythmias](#)

2)) Summary: [Formoterol](#) may prolong the QT interval, therefore concomitant use with other drugs that prolong the QT interval should be approached with caution due to additive effects on the QT interval and the potential for increased risk of [ventricular arrhythmias](#) [112]. Monitoring for QT interval prolongation may be warranted if [formoterol](#) and QT prolonging drugs are used concurrently.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Use extreme caution with concomitant administration of [formoterol](#) and QT prolonging drugs, such as [fluoxetine](#), [methadone](#), or [nilotinib](#), as this may result in additive effects on the QT interval and may increase the risk of [ventricular arrhythmias](#) [112]. If coadministration is required, QT interval monitoring may be warranted.

7)) Probable Mechanism: additive effects on QT interval

3.5.1.AX] [Gatifloxacin](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and drugs that may prolong the QT interval, such as [gatifloxacin](#) [2]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and drugs that may prolong the QT interval, such as [gatifloxacin](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.AY] Gemifloxacin

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Concomitant use of gemifloxacin and other QT prolonging drugs, such as asenapine, may increase the risk of QT interval prolongation and should be avoided [14]. Geriatric patients may be particularly sensitive to QT prolongation [92]. If concurrent therapy is required, closely monitor for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of asenapine and gemifloxacin, both drugs that prolong the QT interval, may increase the potential for serious cardiovascular effects and should be avoided [14]. Geriatric patients may be particularly sensitive to QT prolongation [92]. If concomitant therapy is required, closely monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AZ] Gonadorelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs [113] [114] [115]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur [113] [114] [115].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.BA] Goserelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs [113] [114] [115]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur [113] [114] [115].
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.BB| [Granisetron](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and drugs that may prolong the QT interval, such as [granisetron](#) [2] [70]. However, if concurrent therapy is required, monitor carefully for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of asenapine with [granisetron](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BC| [Halofantrine](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: Both asenapine and [halofantrine](#) may prolong QT interval. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and drugs that may prolong the QT interval, such as [halofantrine](#) [2] [51]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. [Halofantrine](#) has been shown to prolong the QT interval at the recommended therapeutic dose and serious [arrhythmias](#) have been reported [51]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and [halofantrine](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2] [51]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.BD| [Haloperidol](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: Coadministration of asenapine with other antipsychotic drugs associated with QT-interval prolongation (eg, amisulpride, [haloperidol](#), [risperidone](#)) should be avoided as additive QT prolongation may occur [2]. If concurrent use of asenapine with another antipsychotic known to prolong the QT interval is required, monitor for QT-interval prolongation.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of asenapine with other drugs that prolong the QT interval, such as antipsychotic agents (eg, amisulpride, [haloperidol](#), [risperidone](#)), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. If concurrent therapy is required, monitor patient closely for QT-interval prolongation.
- 7)) Probable Mechanism: additive effects on QT interval

3.5.1.BE] [Histrelin](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs [113] [114] [115]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur [113] [114] [115].
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.BF] [Hydroquinidine](#)

- 1)) Interaction Effect: increased risk of QT interval prolongation
- 2)) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class IA antiarrhythmic drugs known for QT prolongation (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) should be avoided . In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of asenapine with class IA antiarrhythmics (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) 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](#) [2]. 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.BG] [Ibutilide](#)

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

2)) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

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

3.5.1.BH] Iloperidone

1)) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2)) Summary: Both asenapine and iloperidone may prolong the QT interval. Due to the potential for additive effects on QT interval prolongation and increased risk of [torsade de pointes](#), avoid the concomitant use of iloperidone and asenapine [14] [73]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of asenapine and iloperidone may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) and should be avoided [14] [72]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

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

8)) Literature Reports

a)) In an electrocardiographic study of 151 clinically stable patients, the administration of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 milliseconds (msec) increases in QTc interval compared with placebo. QTc interval increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [14].

b)) 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 milliseconds [72].

3.5.1.BI] Imipramine

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

2)) Summary: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events. Additionally asenapine is a weak CYP2D6 inhibitor and [14] [imipramine](#) is a CYP2D6 substrate [34].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6) Clinical Management: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [imipramine](#), should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events [14].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BJ] Ivabradine

1) Interaction Effect: increased risk of QT prolongation

2) Summary: Ivabradine is associated with QT-interval prolongation. Concomitant administration of ivabradine with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval and should be avoided. If concomitant use is required, close cardiac monitoring is necessary [76] [77]. Consider a baseline ECG and on-treatment monitoring.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of ivabradine and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation effects on the QT interval and should be avoided. If concomitant use is required, close cardiac monitoring is necessary [76] [77]. Consider a baseline ECG and on-treatment monitoring.

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BK] [Ketoconazole](#)

1) Interaction Effect: increased risk for 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 asenapine with a QT prolonging agent such as [ketoconazole](#) should be avoided. In an ECG study of 151 clinically stable patients, administration of asenapine in doses of 5, 10, 15, and 20 mg twice daily resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc interval increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [7]. If concomitant use is required, the patient should be closely monitored for prolongation of the QT interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Using asenapine together with a QT prolonging agent such as [ketoconazole](#) should be avoided, as concomitant use may result in additive effects on the QT interval and increased risk for [torsades de pointes](#) [7]. If concomitant use is required, the patient should be closely monitored for prolongation of the QT interval.

7) Probable Mechanism: additive effect on QT interval

3.5.1.BL] Lapatinib

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

2) Summary: Concomitant use of asenapine and lapatinib, both drugs that prolong the QT interval, is not recommended due to the potential for additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#) [14].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and lapatinib, both drugs that prolong the QT interval, is not recommended due to the potential for additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#) [14].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BM] [Leuprolide](#)

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs [113] [114] [115]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur [113] [114] [115].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BN] [Levofloxacin](#)

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 asenapine with [levofloxacin](#) should be avoided. In an ECG study of 151 clinically stable patients, administration of asenapine in doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc interval increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. Rare cases of QT prolongation and [torsade de pointes](#) have been reported during postmarketing use of [levofloxacin](#) [50]. If concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and [levofloxacin](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2] [50]. 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.BO] [Lopinavir](#)

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

2) Summary: Postmarketing cases of QT interval prolongation and [torsade de pointes](#) have been reported with [lopinavir/ritonavir](#). Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of [lopinavir/ritonavir](#) with other drugs that prolong the QT interval [25], such as asenapine [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of [lopinavir/ritonavir](#) with other drugs that prolong the QT interval, such as asenapine, as coadministration may result in additive effects on QT-interval prolongation and an increased risk of [torsade de pointes](#) [25] [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BP] 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, including asenapine, should be avoided. If concomitant administration with artemether/lumefantrine and asenapine is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy due to the long half-life of lumefantrine (3 to 6 days) [101].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid coadministration of artemether/lumefantrine with drugs that prolong the QT interval, including asenapine, due to the potential for additive effects on QT-interval prolongation. If concomitant administration of artemether/lumefantrine and asenapine is medically required, use caution and monitor the ECG. Additionally, caution is advised when administering drugs that prolong the QT interval after completing artemether/lumefantrine therapy due to the long half-life of lumefantrine (3 to 6 days) [101].

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

3.5.1.BQ] Mefloquine

1) Interaction Effect: increased risk of QT prolongation

2) Summary: Both asenapine and [mefloquine](#) use have been associated with QT interval prolongation [2] [53]. In an electrocardiographic study of 151 clinically stable patients, administration of asenapine in doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc interval increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. If concurrent therapy with asenapine and [mefloquine](#) is required, monitor patient closely for prolongation of the QT interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine with [mefloquine](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [14] [53]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

7) Probable Mechanism: additive effect on QT interval

3.5.1.BR] Mesoridazine

1) Interaction Effect: an increased risk of QT interval prolongation, [ventricular arrhythmias](#), and [torsade de pointes](#)

2) Summary: Concomitant use of asenapine and [mesoridazine](#) can additively prolong the QT interval [14] and increase the risk of [ventricular arrhythmias](#) and [torsade de pointes](#). Therefore, coadministration of asenapine and [mesoridazine](#) is contraindicated [71].

- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of asenapine and [mesoridazine](#) is not common clinical practice. However, coadministration of asenapine and [mesoridazine](#) is contraindicated due to the potential for serious side effects including life threatening prolongation of the QT interval and increased risk for [torsade de pointes](#) and/or sudden death [71].
- 7J) Probable Mechanism: additive effects on the QT interval

3.5.1.BS] [Methadone](#)

- 1J) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2J) Summary: Both asenapine and [methadone](#) may prolong QT interval [49]. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and [methadone](#) [2]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc intervals increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. Cases of QT interval prolongation and serious [arrhythmias](#), including [torsades de pointes](#), have also been reported with [methadone](#) use. [49]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of asenapine and [methadone](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7J) Probable Mechanism: additive effects on QT interval

3.5.1.BT] [Metoclopramide](#)

- 1J) Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)
- 2J) Summary: Concomitant use of [metoclopramide](#) with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated [88]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions. Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [89].
- 3J) Severity: contraindicated
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [metoclopramide](#) with antipsychotic agents is contraindicated [88]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [89].
- 7J) Probable Mechanism: unknown

3.5.1.BU] [Metronidazole](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation and [arrhythmias](#)
- 2) Summary: Concurrent use of [metronidazole](#) with other QT-prolonging drugs was a probable cause of QT-interval prolongation in one study of cardiac ICU patients. Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs [27].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [metronidazole](#) with other QT interval-prolonging drugs, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur. Consider close [ECG monitoring](#) at baseline and during concurrent therapy with QT-interval prolonging drugs [27].
- 7) Probable Mechanism: additive QT-interval prolongation
- 8) Literature Reports

a) In a retrospective study, 164 of 501 patients admitted in cardiac ICUs (87.7%) developed QT-interval prolongation potentially linked to inhibition of CYP450-mediated metabolism. Out of 1027 total interactions that were potentially associated with QT-interval prolonging effects, interactions with [metronidazole](#) (n=22) were some of the most common. No patients developed [torsades de pointes](#) during their ICU stays. Close [ECG monitoring](#) at baseline and during concurrent therapy with drugs known to cause QT-interval prolongation is recommended [27].

b) A 71-year-old woman with antibiotic-induced [pseudomembranous colitis](#) developed ECG QTc interval prolongation and [torsades de pointes](#) with concurrent [amiodarone](#) 450 mg bolus followed by 900 mg/day IV and [metronidazole](#) 1500 mg/day oral administration. Baseline QTc interval was 440 msec. [Amiodarone](#) was added after trial fibrillation developed with 3 days of [amiodarone](#) therapy. Conversion to sinus rhythm occurred 2 days later; however, the follow-up ECG revealed a QTc interval of 625 msec. Symptoms progressed to sustained torsades de pointes-variant [ventricular tachycardia](#) that required emergent [cardioversion/defibrillation](#) to restore normal sinus rhythm. [Amiodarone](#) and [metronidazole](#) were immediately withdrawn, and the QTc interval slowly returned to baseline values without further clinically significant [arrhythmia](#) events [28].

3.5.1.BV] [Mifepristone](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of asenapine with [mifepristone](#) (Korlym(TM)) should be avoided as both agents are associated with QT-interval prolongation, and coadministration may result in additive QT prolongation [47] [14]. Due to the long half-life of [mifepristone](#), at least 2 weeks should elapse between [mifepristone](#) (Korlym(TM)) discontinuation and asenapine initiation. If concurrent therapy is required, use the lowest effective dose; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing asenapine dosage [47]. Monitor closely for prolongation of the QT interval.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of asenapine with [mifepristone](#) due to the potential for additive effects on QT-interval prolongation [14] [47]. Based on the long half-life of [mifepristone](#), wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before starting asenapine. If concomitant use

is required, use the lowest effective dose; additionally, wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before increasing asenapine [47]. Monitor closely for prolongation of the QT interval.

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

3.5.1.BW] [Morphine](#)

1J) Interaction Effect: increased risk of CNS depression

2J) Summary: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant [morphine](#) and other CNS depressants for hypotension, [respiratory depression](#) and sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs [107] [108] [109].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, [respiratory depression](#) or sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs [107] [108] [109].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.BX] [Morphine Sulfate Liposome](#)

1J) Interaction Effect: increased risk of CNS depression

2J) Summary: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant [morphine](#) and other CNS depressants for hypotension, [respiratory depression](#) and sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs [107] [108] [109].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, [respiratory depression](#) or sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs [107] [108] [109].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.BY] [Moxifloxacin](#)

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

2J) Summary: Both asenapine and [moxifloxacin](#) have been associated with QT prolongation [2] [57]. In an ECG study of 151 clinically stable patients, administration of asenapine in doses of 5, 10, 15, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc interval increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline

measurements were not experienced by any patient [2]. Cases of QT interval prolongation and serious arrhythmias, including *torsade de pointes*, have also been reported with *moxifloxacin* use. Due to the potential for additive QT interval effects and serious complications, use caution when these drugs are administered concomitantly and do not exceed the recommended dose or infusion rate of *moxifloxacin* [57].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when asenapine and *moxifloxacin* are coadministered [14] [57] as this may increase the risk of cardiac adverse events, including *torsade de pointes*. Do not exceed the recommended dose or infusion rate of *moxifloxacin* when asenapine is coadministered [57].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.BZ| *Nafarelin*

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

2) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs [113] [114] [115]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of *cardiac toxicity*, including changes in the ECG.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur [113] [114] [115].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.CA| *Nilotinib*

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

2) Summary: Concomitant use of asenapine and nilotinib, both QT prolonging drugs, should be avoided [14]. Coadministration may increase the potential for additive effects on the QT interval and increased risk of *torsade de pointes*. However, if coadministration is required, the patient should be closely monitored for prolongation of the QT interval [80].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine and nilotinib, both 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 [80].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CB| *Norfloxacin*

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

2) Summary: Concomitant use of asenapine and other QT prolonging drugs, such as *norfloxacin* [91], may increase the risk of QT interval prolongation and should be avoided [14]. Geriatric patients may be

particularly sensitive to QT prolongation [91]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine and [norfloxacin](#), both drugs that prolong the QT interval, may increase the potential for serious cardiovascular effects and should be avoided [14]. Geriatric patients may be particularly sensitive to QT prolongation [91]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.CC] [Nortriptyline](#)

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

2) Summary: Asenapine has been associated with QT prolongation. Due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#), concomitant use of asenapine with [nortriptyline](#) should be avoided [14].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine with [nortriptyline](#) should be avoided due to the potential for additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [14]. However, if concurrent therapy is required, monitor ECG closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) In a electrocardiographic assessment in clinically stable patients with [schizophrenia](#) (n=151), QT interval increased 2 to 5 milliseconds with asenapine compared with placebo at doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily. No patients experienced QT interval increases of 60 milliseconds or more from baseline or [torsade de pointes](#). Reports of QT intervals of 500 milliseconds or more occurred at rates comparable to placebo [14].

3.5.1.CD] [Octreotide](#)

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

2) Summary: Concurrent use of asenapine with other QT prolonging drugs, such as [octreotide](#) [18], should be avoided due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [14]. If concurrent therapy is required, monitor ECG for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine and [octreotide](#) should be avoided due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [14]. If concurrent therapy is required, monitor ECG for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CE] [Ofloxacin](#)

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

2) Summary: Concomitant use of [ofloxacin](#) and other QT prolonging drugs, such as asenapine, should be avoided [14]. Concurrent use of asenapine and [ofloxacin](#) may increase the risk of QT interval prolongation

due to additive effects on the QT interval. Because geriatric patients may be particularly sensitive to QT prolongation associated with drug effects, appropriate precautions should be taken when coadministering these drugs to this patient population [35]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine and [ofloxacin](#), both drugs that prolong the QT interval should be avoided [14], as it may increase the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Because geriatric patients may be particularly sensitive to QT prolongation associated with drug effects, take appropriate precautions when coadministering these drugs to this patient population [35]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.CF| [Ondansetron](#)

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

2) Summary: Concomitant use of asenapine and [ondansetron](#), both drugs that prolong the QT interval, may result in additive effects on QT interval prolongation and an increased risk of serious [ventricular arrhythmias](#) [2] [116]. In an electrocardiographic study of 151 clinically stable patients, administration of asenapine 5 mg, 10 mg, 15 mg, and 20 mg twice daily doses resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc interval increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. QT prolongation, predominantly with IV administration, has been reported with [ondansetron](#) use [117]. Therefore, caution should be used when these agents are given concurrently, and if concurrent therapy is required, [ECG monitoring](#) is recommended [116].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine with [ondansetron](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [116] [14]. However, if concurrent therapy is required, [ECG monitoring](#) is recommended [116].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CG| [Oxycodone](#)

1) Interaction Effect: increased risk of CNS depression

2) Summary: Use caution with concomitant use of the CNS depressant [oxycodone](#) with another CNS depressant, as additive CNS depressant effects, such as [respiratory depression](#), hypotension, and profound sedation, can progress to coma or death. Assess the duration of use and degree of tolerance to CNS depressants (including alcohol and illicit drugs) before concurrent use. If coadministration is clinically necessary, decrease the dose of 1 or both drugs. Monitor patients for sedation, [respiratory depression](#), and hypotension, especially with therapy initiation and dose changes [43].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with concomitant use of [oxycodone](#) with another CNS depressant, as additive CNS depressant effects, such as [respiratory depression](#), hypotension, and profound sedation, can progress to coma or death. Assess the duration of use and degree of tolerance to CNS depressants

(including alcohol and illicit drugs) before concurrent use. If coadministration is clinically necessary, decrease the dose of 1 or both drugs. Monitor patients for sedation, [respiratory depression](#), and hypotension, especially with therapy initiation and dose changes [43].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.CHJ [Oxymorphone](#)

1J) Interaction Effect: increased risk of [respiratory depression](#), profound sedation, coma, and death

2J) Summary: Coadministration of [oxymorphone](#) and a CNS depressant may result in additive respiratory and CNS depressant effects and an increased risk of [respiratory depression](#), profound sedation, coma, and death. If concurrent use is clinically necessary, initiate [oxymorphone](#) at a dose of 5 mg every 12 hours. Monitor patients for sedation, hypotension, and [respiratory depression](#), and consider reducing the CNS depressant dose [102].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [oxymorphone](#) and a CNS depressant may result in additive respiratory and CNS depressant effects. If concurrent use is clinically necessary, initiate [oxymorphone](#) at a dose of 5 mg every 12 hours. Monitor patients for sedation and [respiratory depression](#), sedation, and hypotension, and consider reducing the CNS depressant dose [102].

7J) Probable Mechanism: additive respiratory and CNS depressant effects

3.5.1.CIJ [Paliperidone](#)

1J) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2J) Summary: Both asenapine and [paliperidone](#) may prolong QT interval. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and [paliperidone](#) [2] [119] [120]. However, if concurrent therapy is required, monitor carefully for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of asenapine and [paliperidone](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2] [119] [120]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.CJ [Paroxetine](#)

1J) Interaction Effect: increased exposure to [paroxetine](#)

2J) Summary: [Paroxetine](#) exposure increased approximately 2-fold after a single 20-mg dose of [paroxetine](#) during treatment with asenapine 5 mg twice daily in healthy male subjects (n=15). Concomitant use of asenapine and [fluvoxamine](#) should be used with caution [2].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Concomitant use of asenapine and [paroxetine](#) should be used with caution [2].

7J) Probable Mechanism: inhibition of CYP2D6-mediated [paroxetine](#) metabolism

8J) Literature Reports

a) **Paroxetine** exposure increased approximately 2-fold during treatment with asenapine 5 mg twice daily in healthy male subjects (n=15) administered a 20-mg once daily dose of **paroxetine** for 9 days. The C_{max} and AUC of asenapine decreased by 13% and 9%, respectively, after a single 5-mg dose of asenapine in healthy volunteers administered **paroxetine** 20 mg once daily for 9 days. Asenapine is a weak CYP2D6 inhibitor [2].

3.5.1.CK] Pasireotide

- 1) Interaction Effect: increased risk of QT prolongation
- 2) Summary: Pasireotide is associated with QT-interval prolongation. In 2 studies, QT prolongation occurred at both therapeutic and supratherapeutic doses of pasireotide. Concomitant administration of pasireotide with other drugs that prolong the QT interval, including antiarrhythmic medications, may have additive prolonging effects on the QT interval. A baseline ECG and on-treatment monitoring are recommended when pasireotide is coadministered with other QT-prolonging agents [78].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of pasireotide and QT-prolonging drugs, including antiarrhythmic medications, may result in additive prolongation effects on the QT interval. A baseline ECG and on-treatment monitoring are recommended when pasireotide is coadministered with other QT-prolonging agents [78].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.CL] Pazopanib

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Both asenapine [2] and pazopanib [66] have been associated with QT interval prolongation. Due to the potential for additive effects on the QT interval, avoid the concomitant use of asenapine and other QT-prolonging drugs [2], such as pazopanib. If concomitant use is required, close monitoring of cardiac function is warranted.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant use of asenapine and other QT-prolonging drugs [2], such as pazopanib [66]. If concurrent therapy is required, monitor cardiac function closely.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.CM] Perflutren Lipid Microsphere

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Both asenapine and perflutren may prolong the QT interval [14] [22]. Additionally, serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren [22]. Therefore, coadministration of asenapine and other QT prolonging drugs, such as perflutren, should be avoided due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [14]. If concurrent therapy is required, monitor closely for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Avoid coadministration of asenapine and perflutren [22] due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects [14]. If concurrent therapy is required, monitor closely for QT interval prolongation.

7) Probable Mechanism: additive effects on the QT interval

8) Literature Reports

a) Serious cardiopulmonary reactions, including fatalities, have been reported during or after administration of perflutren-containing microspheres; most serious reactions occurred within 30 minutes of administration. In 221 subjects receiving a perflutren-containing microsphere bolus injection of up to 10 microL/kg, measurement of ECG parameters from 1 hour to 72 hours after administration revealed QTc prolongations of greater than 30 milliseconds in 29% (64/221) of subjects. Among 46 subjects who were further evaluated, 39% experienced associated cardiac rhythm changes. The effects of concomitant drugs on ECG changes has not been studied [22].

3.5.1.CN] Pimozide

1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2) Summary: [Pimozide](#) prolongs the QT interval. An additive effect on the QT interval can be expected when [pimozide](#) is coadministered with a drug that prolongs the QT interval, such as asenapine [2]. Therefore the concurrent administration of [pimozide](#) and asenapine is contraindicated [121].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of [pimozide](#) and a drug that prolongs the QT interval, such as asenapine, is contraindicated [121].

7) Probable Mechanism: additive effects on QT interval

3.5.1.CO] Piperaquine

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

2) Summary: Concomitant administration of piperaquine (a QT-interval prolonging drug) with other drugs that cause QT-interval prolongation, including antiarrhythmic medications, is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating (based on the half-life) at the time of piperaquine administration, is contraindicated [74].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of piperaquine (a QT-interval prolonging drug) with other drugs that cause QT-interval prolongation, including antiarrhythmic medications, is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating (based on the half-life) at the time of piperaquine administration, is contraindicated [74].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.CP] Pirmenol

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class IA antiarrhythmic drugs known for QT prolongation (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval

compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of asenapine with class IA antiarrhythmics (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) 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](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

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

3.5.1.CQJ [Posaconazole](#)

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

2J) Summary: In an ECG study of 151 clinically stable patients, administration of asenapine in doses of 5, 10, 15, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc interval increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient. Use of [posaconazole](#) has also been associated with QT interval prolongation and [torsade de pointes](#) has been reported on rare occasions with [posaconazole](#) therapy. Due to the potential for additive effects on the QT interval and increased risk of serious cardiovascular effects, caution is advised if these agents are coadministered [14] [21]. If concurrent therapy is required, monitoring for QT interval prolongation may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when [posaconazole](#) is given concomitantly with other drugs that may prolong the QT interval, such as asenapine [14], as this may result in additive effects on the QT interval and an increased risk of serious cardiovascular effects [21]. If concurrent therapy is required, monitoring for QT interval prolongation may be warranted.

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

3.5.1.CRJ [Prajmaline](#)

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

2J) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class IA antiarrhythmic drugs known for QT prolongation (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of asenapine with class IA antiarrhythmics (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) 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](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

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

3.5.1.CSJ [Procainamide](#)

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class IA antiarrhythmic drugs known for QT prolongation (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of asenapine with class IA antiarrhythmics (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) 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](#) [2]. 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.CT] [Prochlorperazine](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Asenapine has been associated with QT interval prolongation [2] and [prochlorperazine](#) is a phenothiazine tranquilizer and some drugs in this class have been associated with distortions of the QT interval [87]. Due to the potential for additive effects on the QT interval, avoid the coadministration of asenapine and [prochlorperazine](#) [2]. If concurrent therapy is required, monitor cardiac function closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant use of asenapine with other drugs that prolong the QT interval, such as [prochlorperazine](#), as coadministration may result in additive effects on QT interval prolongation [2]. If concurrent therapy is required, monitor cardiac function closely.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CU] [Promethazine](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Asenapine has been associated with QT interval prolongation. Due to the potential for additive effects on the QT interval, the coadministration of asenapine with other drugs that may prolong the QT interval, such as [promethazine](#), should be avoided [2]. If coadministration is required, monitor for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid the concomitant use of asenapine with other drugs that may prolong the QT interval, such as [promethazine](#), as coadministration may result in additive effects on QT interval prolongation [2]. If coadministration is required, monitor for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CV] [Propafenone](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: Both asenapine and [propafenone](#) may prolong QT interval. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine

and [propafenone](#). Additionally asenapine is a weak 2D6 inhibitor [2] and [propafenone](#) is both a inhibitor and substrate for the 2D6 isoenzyme [95]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and [propafenone](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval

8) Literature Reports

a) In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. Cases of QT interval prolongation and serious [arrhythmias](#), including [torsades de pointes](#), have also been associated with [propafenone](#) use [95].

3.5.1.CW] [Protriptyline](#)

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

2) Summary: Asenapine has been associated with QT interval prolongation [2]. [Protriptyline](#) has a tendency to produce [arrhythmias](#) and prolongation of conduction time [93]. Additionally asenapine is a weak CYP2D6 inhibitor and [14] [protriptyline](#) is a CYP2D6 substrate [93]. Due to the potential for additive effects on the QT interval, avoid the coadministration of asenapine and [protriptyline](#) [2]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid the concomitant use of asenapine with other drugs that prolong the QT interval, such as [protriptyline](#), as coadministration may result in additive effects on QT interval prolongation [2]. If coadministration is required, monitoring for QT interval prolongation may be warranted.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.CX] [Quetiapine](#)

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

2) Summary: The concomitant use of [quetiapine](#) with a QT-prolonging drug should be avoided. [Quetiapine](#) is known to increase the QT interval and concurrent use with another drug known to prolong the QT interval may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#) [39] [40]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [quetiapine](#) with a drug known to prolong the QT interval should be avoided, as concurrent use of such agents may lead to an increased risk of serious cardiac adverse events, including [torsade de pointes](#) [39] [40]. If concurrent therapy is required, monitor carefully for QT-interval prolongation and dosage adjustment of [quetiapine](#) may be necessary.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.CY| Quinidine

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

2J) Summary: The concomitant use of asenapine with class IA antiarrhythmic drugs, such as [quinidine](#), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#). In an electrocardiographic study of 151 clinically stable patients, the administration of asenapine in doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc intervals increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [14]. If concurrent therapy with asenapine and [quinidine](#) is required, monitor patient closely for prolongation of the QT interval.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of asenapine with class IA antiarrhythmics, such as [quinidine](#), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [14]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

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

3.5.1.CZ| Quinine

1J) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2J) Summary: Both asenapine and [quinine](#) may prolong QT interval. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and [quinine](#) [2] [61]. However, if concurrent therapy is required, monitor carefully for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of asenapine and [quinine](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2] [61]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7J) Probable Mechanism: additive effects on QT interval

3.5.1.DA| Ranolazine

1J) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2J) Summary: Both asenapine and [ranolazine](#) may prolong QT interval [2] [123]. [Ranolazine](#) prolongs the QT interval in a dose-dependent manner [123]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and [ranolazine](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DB| [Risperidone](#)

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

2) Summary: Coadministration of asenapine with other antipsychotic drugs associated with QT-interval prolongation (eg, amisulpride, [haloperidol](#), [risperidone](#)) should be avoided as additive QT prolongation may occur [2]. If concurrent use of asenapine with another antipsychotic known to prolong the QT interval is required, monitor for QT-interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine with other drugs that prolong the QT interval, such as antipsychotic agents (eg, amisulpride, [haloperidol](#), [risperidone](#)), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. If concurrent therapy is required, monitor patient closely for QT-interval prolongation.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DC| [Salmeterol](#)

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

2) Summary: Both asenapine and salmeterol may prolong the QT interval [14] [68]. Due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#), concomitant use should be avoided [14]. If coadministration is required, monitor carefully for QT interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine and salmeterol, both drugs that prolong the QT interval [68] [14], should be avoided due to the potential for additive effects on QT interval prolongation and an increased risk of serious cardiac events, including [torsade de pointes](#) [14]. If concomitant therapy is required, closely monitor ECG for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.DD| [Saquinavir](#)

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

2) Summary: Due to the potential for additive effects on the QT interval, concomitant use of asenapine and ritonavir-boosted [saquinavir](#) should be considered only when no alternatives are available and the potential benefits outweigh the potential risks. Prolongation of the QT and PR intervals have been observed with ritonavir-boosted [saquinavir](#) therapy and rare cases of [torsades de pointes](#) have been reported in postmarketing evaluations [97]. In an electrocardiographic study of 151 clinically stable patients, the effect of asenapine doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc interval increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy,

if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either [haloperidol](#) or ritonavir-boosted [saquinavir](#) or both [97].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if ritonavir-boosted [saquinavir](#) is coadministered with other drugs that prolong the QT interval, such as asenapine [2] [97]. These drugs should be used concomitantly only when no alternatives are available and the potential benefits outweigh the potential risks. Do not initiate concomitant therapy in patients with a baseline QT interval of greater than 450 milliseconds. In patients with a baseline QT interval of less than 450 milliseconds, perform an on-treatment ECG approximately 3 to 4 days after therapy is initiated. During concomitant therapy, if a subsequent QT interval reading is greater than 480 milliseconds or has increased by more than 20 milliseconds from baseline, evaluate whether to discontinue either asenapine or ritonavir-boosted [saquinavir](#) or both [97].

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.DE] Sematilide

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

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DF] Sertindole

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

2) Summary: Coadministration of asenapine with other antipsychotic drugs associated with QT-interval prolongation (eg, amisulpride, [haloperidol](#), [risperidone](#)) should be avoided as additive QT prolongation may occur [2]. If concurrent use of asenapine with another antipsychotic known to prolong the QT interval is required, monitor for QT-interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine with other drugs that prolong the QT interval, such as antipsychotic agents (eg, amisulpride, [haloperidol](#), [risperidone](#)), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. If concurrent therapy is required, monitor patient closely for QT-interval prolongation.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DG| Sevoflurane

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#) [32].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Sevoflurane](#) is a QT-interval-prolonging drug. Use caution with concurrent use of other QT-interval-prolonging agents, due to increased risk of additive QT-interval prolongation and [torsade de pointes](#) [32].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.DH| Sodium Phosphate

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: The concomitant use of asenapine with [sodium phosphate](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [41] [14]. Prolongation of QT interval, associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)), and rare but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [41]. In an electrocardiographic study of 151 clinically stable patients, administration of asenapine in doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc intervals increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [14]. If coadministration of [sodium phosphate](#) and asenapine is required, pre-dose and post-colonoscopy ECGs should be considered [41].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when asenapine and [sodium phosphate](#) are coadministered as this may increase the risk of cardiac adverse events, including [torsade de pointes](#) [41] [14]. If coadministration of [sodium phosphate](#) and asenapine is required, pre-dose and post-colonoscopy ECGs should be considered [41].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.DI| Sodium Phosphate, Dibasic

- 1) Interaction Effect: increased risk of QT interval prolongation
- 2) Summary: The concomitant use of asenapine with [sodium phosphate](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [41] [14]. Prolongation of QT interval, associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)), and rare but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [41]. In an electrocardiographic study of 151 clinically stable patients, administration of asenapine in doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc intervals increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [14]. If coadministration of [sodium phosphate](#) and asenapine is required, pre-dose and post-colonoscopy ECGs should be considered [41].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6J) Clinical Management: Use caution when asenapine and [sodium phosphate](#) are coadministered as this may increase the risk of cardiac adverse events, including [torsade de pointes](#) [41] [14]. If coadministration of [sodium phosphate](#) and asenapine is required, pre-dose and post-colonoscopy ECGs should be considered [41].

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

3.5.1.DJ] [Sodium Phosphate](#), Monobasic

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

2J) Summary: The concomitant use of asenapine with [sodium phosphate](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [41] [14]. Prolongation of QT interval, associated with [electrolyte imbalances](#) (eg, hypokalemia and [hypocalcemia](#)), and rare but serious reports of [arrhythmias](#) have been noted with [sodium phosphate](#) therapy [41]. In an electrocardiographic study of 151 clinically stable patients, administration of asenapine in doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc intervals increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [14]. If coadministration of [sodium phosphate](#) and asenapine is required, pre-dose and post-colonoscopy ECGs should be considered [41].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution when asenapine and [sodium phosphate](#) are coadministered as this may increase the risk of cardiac adverse events, including [torsade de pointes](#) [41] [14]. If coadministration of [sodium phosphate](#) and asenapine is required, pre-dose and post-colonoscopy ECGs should be considered [41].

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

3.5.1.DK] [Solifenacin](#)

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

2J) Summary: Due to the potential for additive effects on QT interval prolongation and risk of [torsade de pointes](#), the concomitant use of asenapine with other QT interval-prolonging drugs, such as [solifenacin](#) [98], should be avoided [2]. If concomitant use is required, close monitoring of cardiac function may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid the concomitant use of asenapine with other drugs that prolong the QT interval, such as [solifenacin](#) [98], as coadministration may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [2]. If concurrent therapy is required, monitor cardiac function closely.

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

3.5.1.DL] [Sorafenib](#)

1J) Interaction Effect: increased risk of QT interval prolongation and risk of [ventricular arrhythmias](#)

2J) Summary: Both asenapine and [sorafenib](#) have been associated with QT prolongation and concomitant use should be avoided [14]. Although this interaction has not been evaluated, the concomitant use of asenapine with [sorafenib](#) may increase the risk of prolonged QT interval and [ventricular arrhythmias](#). If concomitant use of asenapine with [sorafenib](#) is required, [monitoring of ECG](#) and electrolytes ([calcium](#), [magnesium](#), and [potassium](#)) is recommended [62].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use asenapine and [sorafenib](#), both QT prolonging drugs, should be avoided [14]. Concurrent use of these agents may increase the risk of cardiac adverse events, including [ventricular arrhythmias](#). If concomitant use of asenapine with [sorafenib](#) is required, [monitoring of ECG](#) and electrolytes ([calcium](#), magnesium, and potassium) is recommended [62].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.DM] [Sotalol](#)

- 1) Interaction Effect: an increased risk of QT interval prolongation
- 2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.DN] [Sparfloxacin](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: [Sparfloxacin](#) prolongs the QT interval [99]. An additive effect on the QT interval can be expected when [sparfloxacin](#) is coadministered with a drug that prolongs the QT interval, such as asenapine [2]. Therefore the concurrent administration of [sparfloxacin](#) and asenapine is contraindicated [99].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [sparfloxacin](#) and a drug that prolongs the QT interval, such as asenapine, is contraindicated [99].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.DO] [Sultopride](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Coadministration of asenapine with other antipsychotic drugs associated with QT-interval prolongation (eg, amisulpride, [haloperidol](#), [risperidone](#)) should be avoided as additive QT prolongation may occur [2]. If concurrent use of asenapine with another antipsychotic known to prolong the QT interval is required, monitor for QT-interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine with other drugs that prolong the QT interval, such as antipsychotic agents (eg, amisulpride, [haloperidol](#), [risperidone](#)), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. If concurrent therapy is required, monitor patient closely for QT-interval prolongation.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DP] [Sunitinib](#)

1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)

2) Summary: Both asenapine and [sunitinib](#) may prolong QT interval [48]. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and [sunitinib](#) [2]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. Prolonged QT intervals and [torsade de pointes](#) have been reported in sunitinib-treated patients. If concurrent therapy is required, ECG and [electrolyte monitoring](#) should be considered [48].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and [sunitinib](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DQ] [Suvorexant](#)

1) Interaction Effect: CNS depression

2) Summary: Use caution with coadministration of suvorexant with other CNS depressants due to the risk of additive CNS depressant effects. Cognitive and behavioral changes (eg, hallucinations, anxiety, amnesia, other neuropsychiatric symptoms) and complex sleep behaviors (eg, sleep-driving, preparing and eating food) may also be potentiated. Also alcohol should be avoided during treatment. If coadministration with another CNS depressant is required, dose adjustments of both drugs may be necessary. Concurrent use with other medications that treat insomnia is not recommended, and suvorexant discontinuation may be required if complex sleep behaviors develop [106].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of suvorexant with other CNS depressants due to the risk of additive CNS depressant effects. Cognitive and behavioral changes (eg, hallucinations, anxiety, amnesia, other neuropsychiatric symptoms) and complex sleep behaviors (eg, sleep-driving, preparing and eating food) may also be potentiated. Also alcohol should be avoided during treatment. If coadministration with another CNS depressant is required, dose adjustments of both drugs may be necessary. Concurrent use with other medications that treat insomnia is not recommended, and suvorexant discontinuation may be required if complex sleep behaviors develop [106].

7) Probable Mechanism: additive CNS depression

3.5.1.DR] [Tapentadol](#)

1) Interaction Effect: increased risk of CNS depression

2) Summary: Concomitant use of tapentadol, which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patient's degree of tolerance to CNS depressants. If tapentadol is coadministered with a CNS depressant, initiate the dose of tapentadol ER at 50 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms [respiratory depression](#), hypotension, and sedation [96].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of tapentadol, which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patient's degree of tolerance to CNS depressants. If tapentadol is coadministered with a CNS depressant, initiate the dose of tapentadol ER at 50 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation [96].

7) Probable Mechanism: additive CNS depression effects

3.5.1.DS] Tedisamil

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

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class III antiarrhythmic agents known for QT prolongation (eg, [amiodarone](#), [dofetilide](#), [ibutilide](#), [sotalol](#)) should be avoided . In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and drugs that prolong the QT interval, such as class III antiarrhythmic agents, should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DT] Telavancin

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

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with other drugs known for QT prolongation, such telavancin, should be avoided . In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and drugs known for QT prolongation, such as telavancin, should be avoided due to the potential for additive effects on the QT interval and increased

risk of [torsade de pointes](#) [2]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DU] [Telithromycin](#)

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 asenapine with [telithromycin](#) should be avoided. In an ECG study of 151 clinically stable patients, administration of asenapine in doses of 5, 10, 15, and 20 mg twice daily resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc interval increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2]. QT prolongation and [torsade de pointes](#) have also been reported during postmarketing use of [telithromycin](#) [100]. If concomitant use is required, the patient should be closely monitored for prolongation of the QT interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and [telithromycin](#) should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2] [100]. If concomitant use is required, the patient should be closely monitored for prolongation of the QT interval.

7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.DV] [Terfenadine](#)

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

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with other drugs known for QT prolongation, such as [terfenadine](#), should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 milliseconds increases in QTc interval compared with placebo. QTc intervals increases of 500 milliseconds or more and QTc increases of 60 milliseconds or more from baseline measurements were not experienced by any patient [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and [terfenadine](#) may result in additive effects on the QT interval and an increased risk of [torsade de pointes](#), and therefore should be avoided [2].

7) Probable Mechanism: additive effects on the QT interval

3.5.1.DW] [Tetrabenazine](#)

1) Interaction Effect: increased risk of QT interval prolongation

2) Summary: Asenapine causes an increase in the corrected QT interval. The concomitant use of asenapine with class IA antiarrhythmic drugs known for QT prolongation (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) should be avoided. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of asenapine with class IA antiarrhythmics (eg, [procainamide](#), hydroquinidine, [disopyramide](#)) 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](#) [2]. 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.DX] 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 asenapine should be avoided [110] [14]. However, if concomitant use is required, the patient should be closely monitored for prolongation of the QT interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of tetrabenazine with asenapine should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [110]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) In a randomized, double-blind, placebo controlled crossover study of healthy subjects, a mean increase in QT interval was 9 milliseconds (90% confidence interval, 5 to 10. 4 milliseconds) after a single 50 mg dose of tetrabenazine ([moxifloxacin](#) as a positive control) [110]. In a electrocardiographic assessment in clinically stable patients with [schizophrenia](#) (n=151), QT interval increased 2 to 5 milliseconds compared with placebo at doses of 5 mg, 10 mg, 15 mg, and 20 mg twice daily. No patients experienced QT increases 60 milliseconds or more from baseline or [Torsades de pointes](#). Reports of QT intervals of 500 milliseconds or more occurred at rates comparable to placebo [14].

3.5.1.DY] Thioridazine

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

2) Summary: Coadministration of asenapine with other antipsychotic drugs associated with QT-interval prolongation (eg, amisulpride, [haloperidol](#), [risperidone](#)) should be avoided as additive QT prolongation may occur [2]. If concurrent use of asenapine with another antipsychotic known to prolong the QT interval is required, monitor for QT-interval prolongation.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine with other drugs that prolong the QT interval, such as antipsychotic agents (eg, amisulpride, [haloperidol](#), [risperidone](#)), should be avoided due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#) [2]. If concurrent therapy is required, monitor patient closely for QT-interval prolongation.

7) Probable Mechanism: additive effects on QT interval

3.5.1.DZ] Tizanidine

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

2) Summary: [Tizanidine](#) has the potential to cause QT-interval prolongation [81] [82]. Concomitant administration of [tizanidine](#) with other drugs that prolong the QT interval, including antiarrhythmic

medications, may increase the risk of QT-interval prolongation. Consider a baseline ECG and on-treatment monitoring when [tizanidine](#) is coadministered with other QT interval-prolonging agents.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant administration of [tizanidine](#) and QT interval-prolonging drugs, including antiarrhythmic medications, may result in an increased risk of QT-interval prolongation. Consider a baseline ECG and on-treatment monitoring when [tizanidine](#) is coadministered with other QT interval-prolonging agents.

7J) Probable Mechanism: additive QT interval effects

3.5.1.EA] [Toremifene](#)

1J) Interaction Effect: an increased risk of [Torsade de pointes](#)

2J) Summary: Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), the concomitant use of asenapine with [toremifene](#) should be avoided. If treatment with asenapine is warranted, interrupt [toremifene](#) therapy; however, if coadministration of asenapine with [toremifene](#) can not be avoided, monitor for QT prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT prolongation [26].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [toremifene](#) with asenapine may result in additive effects on the QT interval and should be avoided. If treatment with asenapine is required, interruption of [toremifene](#) is recommended; however, if concomitant use is necessary, closely monitor for QT prolongation. Consider [monitoring ECG](#) at baseline and during treatment as indicated in patients at increased risk of QT prolongation [26].

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

3.5.1.EB] [Trazodone](#)

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

2J) Summary: QT/QTc interval prolongation and postmarketing cases of [torsade de pointes](#) have been reported with [trazodone](#) [75]. Due to the potential for additive effects on QT interval prolongation and risk of [torsade de pointes](#), the concomitant use of asenapine with [trazodone](#) should be avoided [2]. If concomitant use is required, close monitoring of cardiac function may be warranted.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Avoid the concomitant use of asenapine with other drugs that prolong the QT interval, such as [trazodone](#) [75], as coadministration may result in additive effects on QT interval prolongation and an increased risk of [torsade de pointes](#) [2]. If concurrent therapy is required, monitor cardiac function closely.

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

3.5.1.EC] [Trifluoperazine](#)

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

2J) Summary: Asenapine has been associated with QT interval prolongation. Due to the potential for additive effects on the QT interval, avoid the coadministration of asenapine and [trifluoperazine](#) [14]. If concomitant therapy is required, closely monitor for QT interval prolongation.

- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Avoid the concomitant use of asenapine with other drugs that prolong the QT interval, such as [trifluoperazine](#), as coadministration may result in additive effects on QT interval prolongation [14]. If concomitant therapy is required, closely monitor for QT interval prolongation.
- 7)) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.ED] [Trimipramine](#)

- 1)) Interaction Effect: an increased risk of QT interval prolongation
- 2)) Summary: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [trimipramine](#), should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events [14]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of asenapine with other drugs that may cause QT interval prolongation, such as [trimipramine](#), should be avoided due to an increased risk of QT interval prolongation and serious cardiac adverse events [14]. If concurrent therapy is required, closely monitor ECG for QT interval prolongation.
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.EE] [Triptorelin](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs. Androgen deprivation caused by GnRH agonists may prolong the QT interval and cause additive effects when administered with QT-interval prolonging drugs [113] [114] [115]. If concurrent therapy is necessary, monitor patients closely for signs and symptoms of [cardiac toxicity](#), including changes in the ECG.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Use caution with coadministration of gonadotropin-releasing hormone (GnRH) agonists with QT-interval prolonging drugs, as additive effects on the QT interval may occur [113] [114] [115].
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.EF] [Vandetanib](#)

- 1)) Interaction Effect: an increased risk of QT interval prolongation and [Torsades de pointes](#)
- 2)) Summary: The concomitant administration of vandetanib and other drugs that prolong the QT interval, such as asenapine, should be avoided [8]. Vandetanib can prolong the QT interval in a concentration-dependent manner. [Torsades de pointes](#), [ventricular tachycardia](#), and sudden death have been reported in patients taking vandetanib. If these drugs must be coadministered, monitor ECG more frequently. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds. Dosing can then be resumed at a reduced dose [52].
- 3)) Severity: major
- 4)) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine and vandetanib, both drugs that prolong the QT interval, should be avoided [8], as it may result in additive effects on the QT interval and an increased risk of **Torsades de pointes** and **ventricular tachycardia**. If these agents must be given together, monitor ECG more frequently. If the corrected QT interval (Fridericia; QTcF) is greater than 500 milliseconds, discontinue therapy until QTcF returns to less than 450 milliseconds and then resume at a reduced dose [52].

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

3.5.1.EG] Vardenafil

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

2) Summary: Both asenapine and **vardenafil** have been associated with QT prolongation [2] [37] [38]. In an ECG study of 151 clinically stable patients, administration of asenapine in doses of 5, 10, 15, and 20 mg twice daily resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc interval increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient [2]. In 59 healthy males, therapeutic and supratherapeutic doses of **vardenafil** led to QTc interval increases of 4 to 6 milliseconds [37] [38]. If concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of asenapine with **vardenafil** should be avoided due to the potential for additive effects on the QT interval [2] [37] [38]. However, if concurrent therapy is required, monitor patient closely for prolongation of the QT interval.

7) Probable Mechanism: additive effects on QT interval prolongation

8) Literature Reports

a) In a single-dose, double-blind, randomized, placebo- and active-controlled crossover study, 59 male patients receiving **vardenafil** 10 mg (therapeutic), **vardenafil** 80 mg (supratherapeutic), or **moxifloxacin** 400 mg experienced similar increases in QTc interval measurements taken one hour after dosing. Single-dose administration resulted in a placebo-subtracted mean change from baseline QT (uncorrected) of 3 milliseconds (90% confidence interval [CI]: 1, 5) for **moxifloxacin** 400 mg and -2 milliseconds (90% CI: -4, 0) for both **vardenafil** 10 mg and 80 mg. Mean change from baseline Fridericia QT correction was 10 milliseconds (90% CI: 8, 11) for **vardenafil** 80 mg, and 8 milliseconds (90% CI: 6, 9) for both **vardenafil** 10 mg and **moxifloxacin**. Mean change from baseline for individual QT correction was 4 milliseconds (90% CI: 3, 6) for **vardenafil** 10 mg, 6 milliseconds (90% CI: 4, 7) for **vardenafil** 80 mg, and 7 milliseconds (90% CI: 5, 8) for **moxifloxacin**. Mean increases in heart rate with **vardenafil** 10 mg and 80 mg were 5 and 6 beats per minute, respectively, compared with placebo [37] [38].

3.5.1.EH] Vemurafenib

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

2) Summary: Both asenapine and vemurafenib have been associated with QT-interval prolongation [111] [7]. Although this interaction has not been evaluated, coadministration of asenapine with vemurafenib should be avoided due to increased risk of prolonged QT interval and serious cardiac adverse events, including **torsade de pointes** [111]. If concurrent therapy is required, assess baseline electrolytes and ECG and monitor carefully for QT-interval prolongation. Dosage adjustment of vemurafenib may also be warranted.

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid coadministration of asenapine or other QT interval-prolonging drugs with vemurafenib, as additive prolongation effects on the QT interval may result [111] [7]. If concurrent therapy is required, assess baseline electrolytes and ECG and monitor carefully for QT-interval prolongation. Dosage adjustment of vemurafenib may also be warranted.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.EI] Vilanterol

- 1) Interaction Effect: increased risk of [ventricular arrhythmias](#)
- 2) Summary: Vilanterol (a beta-agonist) has potential to prolong the QT interval; therefore, concomitant use with other drugs that can prolong the QT interval may cause an increased risk of [ventricular arrhythmias](#). [Electrocardiograph](#) changes, such as QT-interval prolongation, have been reported with beta-agonists. Use extreme caution during coadministration of vilanterol with a QT-interval prolonging drug or when using vilanterol within 2 weeks of discontinuation of a QT-interval prolonging drug [42]. [ECG monitoring](#) may be warranted if vilanterol and QT-interval prolonging drugs are used concurrently.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of vilanterol and QT-interval prolonging drugs may potentiate cardiovascular effects, such as QT-interval prolongation, and increase the risk of [ventricular arrhythmias](#). Use extreme caution when coadministering vilanterol and QT-interval prolonging drugs, or if using vilanterol within 2 weeks of discontinuation of a QT interval-prolonging drug [42]. If coadministration is required, [ECG monitoring](#) may be warranted.
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.EJ] Vinflunine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Vinflunine is associated with QT-interval prolongation. Concomitant administration of vinflunine with other drugs that prolong the QT interval may have additive prolonging effects on the QT interval and is not recommended [33]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring when vinflunine is coadministered with other QT-prolonging agents.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of vinflunine and QT-prolonging drugs may result in additive QT-interval prolongation effects and is therefore not recommended [33]. If concomitant use is required, consider a baseline ECG and on-treatment monitoring.
- 7) Probable Mechanism: additive QT interval effects

3.5.1.EK] Voriconazole

- 1) Interaction Effect: increased risk of QT interval prolongation and [torsade de pointes](#)
- 2) Summary: Both asenapine and [voriconazole](#) may prolong QT interval [2] [103]. Due to the potential for additive effects on the QT interval and increased risk of [torsade de pointes](#), avoid the concomitant use of asenapine and drugs that may prolong the QT interval, such as [voriconazole](#) [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and drugs that may prolong the QT interval, such as voriconazole [103] may result in additive effects on the QT interval and an increased risk of torsade de pointes, and therefore should be avoided [2]. If concurrent therapy is required, monitor carefully for QT interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.EL] Ziprasidone

- 1) Interaction Effect: increased risk of QT interval prolongation and torsade de pointes
- 2) Summary: Both asenapine and ziprasidone may prolong QT interval. Due to the potential for additive effects on the QT interval and increased risk of torsade de pointes, avoid the concomitant use of asenapine and ziprasidone [2] [104]. In an electrocardiographic study of 151 clinically stable patients, the effect of 5 mg, 15 mg, and 20 mg twice daily of asenapine resulted in 2 to 5 msec increases in QTc interval compared with placebo. QTc intervals increases of 500 msec or more and QTc increases of 60 msec or more from baseline measurements were not experienced by any patient. [2]. Cases of QT interval prolongation and serious arrhythmias, including torsades de pointes, have also been reported with ziprasidone use. [104].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine and ziprasidone may result in additive effects on the QT interval and an increased risk of torsade de pointes, and therefore should be avoided [2] [104].
- 7) Probable Mechanism: additive effects on QT interval

3.5.1.EM] Zotepine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Coadministration of asenapine with other antipsychotic drugs associated with QT-interval prolongation (eg, amisulpride, haloperidol, risperidone) should be avoided as additive QT prolongation may occur [2]. If concurrent use of asenapine with another antipsychotic known to prolong the QT interval is required, monitor for QT-interval prolongation.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of asenapine with other drugs that prolong the QT interval, such as antipsychotic agents (eg, amisulpride, haloperidol, risperidone), should be avoided due to the potential for additive effects on the QT interval and increased risk of torsade de pointes [2]. If concurrent therapy is required, monitor patient closely for QT-interval prolongation.
- 7) Probable Mechanism: additive effects on QT interval

3.5.2] Drug-Food Combinations

3.5.2.A] Ethanol

- 1) Interaction Effect: potentiation of the cognitive and motor effects of alcohol
- 2) Summary: Asenapine may potentiate the cognitive and motor effects of alcohol. Alcoholic beverages should be avoided while taking asenapine [14].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical

6) Clinical Management: Counsel patients on potential for increased risk of central nervous system depression when alcohol is ingested with asenapine. Patients should be instructed to avoid alcohol consumption while taking asenapine [14].

7) Probable Mechanism: additive CNS depression

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

4.1] Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) Improvement in signs and symptoms of [schizophrenia](#) or manic or mixed episodes associated with [bipolar disorder](#) are indicative of efficacy.

B) Toxic

1) Laboratory Parameters

a) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic [monitoring for obesity](#) and [diabetes](#), as listed below [127]:

1) Measure fasting plasma glucose at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of diabetes. Patients with diabetes mellitus should be regularly monitored for worsening of glucose control [127].

2) Measure fasting lipid profile at baseline, at week 12, and then every 5 years thereafter. Repeat testing should be done more frequently as clinically indicated [127].

b) Perform CBC [10] with differential frequently during the first few months in patients with preexisting low WBC or a history of drug-induced [leukopenia/neutropenia](#).

2) Physical Findings

a) Based on available data on the use of atypical antipsychotics, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity developed a consensus position statement that recommends baseline and periodic [monitoring for obesity](#) and [diabetes](#), as listed below [127]:

- 1j) Obtain personal and family history of obesity, diabetes, dyslipidemia, hypertension, and cardiovascular disease prior to treatment and review annually with patient [127].
 - 2j) Track weight and BMI at baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter [127].
 - 3j) Measure waist circumference at baseline, and annually thereafter [127].
 - 4j) Measure blood pressure at baseline, at week 12, then annually thereafter, or more frequently in patients with a higher baseline risk for the development of hypertension [127].
- bj) Monitor orthostatic vital signs in patients predisposed to hypotension [10].
- cj) Examine patient for [tardive dyskinesia](#) before initiation and then annually. Patients at higher risk for [tardive dyskinesia](#) (ie, elderly, patients who have experienced acute dystonic reactions, [akathisia](#), or other clinically significant extrapyramidal side effects) should be examined every 6 months throughout the duration of treatment [128].
- dj) Closely monitor patients for suicidality during therapy due to the increased risk of suicide attempts in patients with [schizophrenia](#) or [bipolar disorder](#) [10].

4.2j Patient Instructions

Aj) Asenapine (By mouth)

Asenapine

Treats [schizophrenia](#) and [bipolar disorder](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction](#) to asenapine.

How to Use This Medicine:

Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

Dry your hands before you handle the tablet.

Do not open the blister pack that contains the tablet until you are ready to take the medicine. Peel back the foil. Then remove the tablet. Do not push the tablet through the foil.

Do not crush, chew, or swallow the tablet. Place the tablet under your tongue and let it melt.

Do not eat or drink anything for at least 10 minutes after you take this medicine.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

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

Some medicines and foods can affect how asenapine works. Tell your doctor if you are taking any of the following:

Blood pressure medicine

[Fluvoxamine](#), [paroxetine](#)

Heart rhythm medicine, such as [amiodarone](#), [procainamide](#), [quinidine](#), [sotalol](#)

Infection medicine, such as [gatifloxacin](#), [moxifloxacin](#)

Medicine to treat mental illness, such as [chlorpromazine](#), [thioridazine](#), [ziprasidone](#)

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have liver disease, [diabetes](#), trouble swallowing, or a history of seizures or [neuroleptic malignant syndrome](#) (NMS). Tell your doctor if you have a blood vessel or heart problem, including low blood pressure, [heart failure](#), heart rhythm problems (such as QT prolongation, slow heartbeat), low potassium or magnesium levels, or a history of a [heart attack](#) or [stroke](#).

This medicine may cause the following problems:

Agitation, irritability, depression, suicidal thoughts, or other abnormal behaviors

A serious condition called [neuroleptic malignant syndrome](#) (NMS)

Heart rhythm changes, such as QT prolongation

[Tardive dyskinesia](#) (a movement disorder) that may not go away after you stop taking this medicine

Asenapine may make you dizzy or drowsy. Do not drive or do anything that could be dangerous until you know how this medicine affects you. Stand up slowly. You may feel lightheaded if you get up suddenly from a lying or sitting position.

This medicine may make you bleed, bruise, or get infections more easily. Take precautions to prevent illness and injury. Wash your hands often.

You might get overheated while you are taking this medicine. Drink more water during hot weather, and while you exercise. Call your doctor if you are too hot and cannot cool down.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

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

[Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Change in how much or how often you urinate

Fast, slow, pounding, or uneven heartbeat

Fever, confusion, increased sweating, severe muscle stiffness, or [loss of bladder control](#)

Jerky muscle movement you cannot control (often in your face, tongue, or jaw)

Lightheadedness, dizziness, or fainting

Mood or behavior changes, or thoughts of hurting yourself or others

Problems with balance or walking

Seizures, unusual tiredness or weakness, pale skin

Shortness of breath or trouble breathing

Swelling in your hands, ankles, feet, or breasts

Trouble speaking or sleeping

Unusual bleeding or bruising

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

Drooling, constipation, vomiting, stomach pain, or upset stomach

Joint or muscle pain

Weight gain

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

4.3] Place In Therapy

A) Asenapine is a psychotropic agent of the dibenzo-oxepino pyrrole class. While the mechanism of action of asenapine is unclear, it is thought to block both the central [dopamine](#) Type 2 (D(2)) and serotonin Type 2 (5HT(2A)) receptors. [2].

B) Asenapine is available as sublingual tablets and is indicated for the acute treatment of [schizophrenia](#) in adults as well as for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. Two 6-week, randomized, double-blind, placebo-controlled, fixed-dose studies demonstrated that asenapine was statistically superior to placebo in adult patients experiencing an acute episode of [schizophrenia](#) and two 3-week, randomized, double-blind, placebo- and active-controlled studies demonstrated that asenapine treatment was statistically superior to placebo in bipolar adult patients experiencing an acute manic or mixed episode with or without psychotic features [2].

4.4] Mechanism of Action / Pharmacology

A) Mechanism of action

1) Asenapine is a psychotropic agent that belongs to the class dibenzo-oxepine pyrroles. It exhibits high affinity for serotonin receptors 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5, 5-HT6, and 5-HT7, [dopamine](#) receptors D1, D2, D3, and D4, alpha adrenergic receptors 1 and 2, and [histamine](#) H1 receptors. Asenapine has moderate affinity for H2 receptors and has very little affinity for muscarinic cholinergic receptors. The exact mechanism by which asenapine exerts its antipsychotic effect is unknown. However, its effect on [schizophrenia](#) may be mediated through a combination of antagonist activity at the [dopamine](#) (D2) and serotonin 5-HT2A receptors [2].

4.5] Therapeutic Uses

4.5.A] Bipolar I disorder, Acute mixed or [manic episodes](#)

FDA Labeled Indication

1) 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](#)

2) Summary:

Asenapine is indicated as monotherapy or adjunctive therapy with either [lithium](#) or [valproate](#) for the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults [1].

Two short-term, randomized, placebo- and active-controlled trials have demonstrated the efficacy of asenapine monotherapy in alleviating symptoms of acute manic or mixed episodes in adult patients with bipolar I disorder [3] [4].

Adjunctive asenapine with either [lithium](#) or [valproate](#) significantly improved mania or mixed episodes compared with placebo at week 3 in a randomized, double-blind, flexible-dose, 12-week study (n=326) [5].

3) Adult:

a) Monotherapy

1) In a 3-week, randomized, placebo-controlled and active-controlled study of patients with acute manic or mixed episodes, patients on asenapine achieved significantly better symptom control compared with placebo. Patients who met DSM-IV criteria for bipolar I disorder and having an acute manic or mixed episode were randomized in a 2:2:1 ratio to asenapine (n=183), [olanzapine](#) (active control; n=203) or placebo (n=94). Asenapine was initiated at 10 mg twice daily and could be decreased to 5 mg twice daily from day 2 onward if necessary. The [olanzapine](#) doses were also flexible, starting with 15 mg on the first day, then could be adjusted to a dose range of 5 to 20 mg once daily. [Olanzapine](#) was included in the study to confirm the sensitivity of the outcome measures, but the study was not designed to analyze potential differences between the asenapine and [olanzapine](#) arms. Patients with rapid-cycling disease, recent [clozapine](#) therapy within the last 12 weeks or previous participation in an asenapine trial were excluded from the trial. All patients had baseline YMRS total scores of at least 20 and duration of the current [manic episode](#) not exceeding 3 months. The mean age of all patients was 38.6 years, 52.7% were male, 68.9% had the diagnosis of a [manic episode](#), and 31.1% had a mixed episode. The mean doses achieved were asenapine 18.4 mg daily and [olanzapine](#) 15.9 mg per day. Patients in the asenapine and [olanzapine](#) arms showed significant improvement in the mean Young Mania Rating Scale (YMRS) total score from baseline to day 21 (primary endpoint) and Clinical Global Impression-Bipolar (CGI-BP) Scale mania severity score compared with the placebo arm (table below). The beneficial effects of asenapine became statistically significant at day 2 and persisted throughout the duration of the study [3].

Mean YMRS total scores and CGI-BP severity scores over 21 days			
	Asenapine	Olanzapine	P
Baseline YMRS total score	29.4	29.7	2
YMRS change +/- SE at day 21	-11.5 +/- 0.8	-14.6 +/- 0.8	-
p-values versus placebo	p less than 0.007	p less than 0.0001	
Baseline CGI-BP severity score	4.6	4.6	4
CGI-BP change +/- SE at day 21	-1.2 +/- 0.1	-1.5 +/- 0.09	-
p-values versus placebo	p=0.012	p less than 0.0001	
Key: YMRS = Young Mania Rating Scale; CGI-BP = Clinical Global Impression-Bipolar; SE = standard error of mean			

Two patients (1 asenapine, 1 olanzapine) committed suicide during the treatment course of the study, on day 11 and day 12, respectively. Asenapine was determined to be "possibly related" to the suicide while olanzapine was considered "unlikely related" to the event. Other serious adverse events occurred in 6.5% of asenapine-treated patients, 7.1% of placebo-treated patients, and 3.9% of olanzapine-treated patients; of which worsening of the disease accounted for the vast majority of the events. Clinically relevant ECG changes occurred in 2 asenapine patients and in 1 olanzapine patient. Relative to placebo, asenapine was associated with higher incidence of somnolence (11.9% vs 3.1%), dizziness (10.3% vs 2%), sedation (8.6% vs 3.1%), weight gain (6.5%

vs 0%), akathisia (5.4% vs 3.1%), and bradykinesia (2.2%). Asenapine-treated patients reporting a 0.9-kg increase in weight compared with 0.1 kg with placebo and 2.6 kg with olanzapine. Significant weight gain (7% or greater increase from baseline weight) occurred in 7.2% of asenapine-treated patients, 1.2% of placebo-treated patients, and 19% of olanzapine-treated patients. Discontinuation rates due to side effects were 9.2%, 4.1%, and 3.4% of the asenapine, placebo, and olanzapine arms, respectively [3].

2b) In a randomized, placebo- and active-controlled study of 3 weeks duration, bipolar I patients with an acute manic or mixed episode who received asenapine experienced greater symptom control compared with placebo. Patients were randomized in a 2:2:1 ratio to asenapine (n=189), [olanzapine](#) (active control; n=188) or placebo (n=103). Asenapine was initiated at 10 mg twice daily and could be decreased to 5 mg twice daily from day 2 onward if necessary. The [olanzapine](#) doses were also flexible, starting with 15 mg on the first day, then could be adjusted to a dose range of 5 to 20 mg daily. [Olanzapine](#) was included for assay sensitivity, but the study was not designed to compare efficacy or safety between the asenapine and [olanzapine](#) arms. Patients with rapid-cycling disease, recent [clozapine](#) therapy within the past 12 weeks or previous participation in an asenapine trial were excluded. All patients had baseline YMRS total scores of at least 20 and current episode lasting 3 months or less. The mean age of all patients was 39.4 years, with 69.3% having a [manic episode](#) and 30.7% having a mixed episode. The mean doses were asenapine 18.2 mg daily and [olanzapine](#) 15.8 mg per day. Patients in the asenapine and [olanzapine](#) arms showed significant improvement in the mean Young Mania Rating Scale (YMRS) total score from baseline to day 21 (primary endpoint) and Clinical Global Impression-Bipolar (CGI-BP) Scale mania severity score compared with the placebo arm (table below). The beneficial effects of asenapine and [olanzapine](#) (compared with placebo) became apparent at day 2, and persisted throughout the duration of the study [4].

Mean YMRS total scores and
CGI-BP severity scores over
21 days

	Asenapine	Olanzapine
Baseline YMRS total score	28.3	28.6
YMRS change +/- SE at day 21	-10.8 +/- 0.8	-12.6 +/- 0.8
p-values versus placebo	p less than 0.0001	p less than 0.0001
Baseline CGI-BP severity score	4.7	4.6
CGI-BP change +/- SE at day 21	-1.2 +/- 0.1	-1.4 +/- 0.1
p-values versus placebo	p less than or equal 0.01	p less than or equal 0.0001
Key: YMRS = Young Mania Rating Scale; CGI-BP = Clinical Global Impression-Bipolar; SE = standard error of mean		

Discontinuation rates due to side effects were 6.2%, 3.8%, and 4.2% in the asenapine, placebo, and olanzapine arms, respectively. Serious adverse effects occurred in 1.5% of asenapine patients (mania in all cases) and 3.8% of placebo patients (mania and akathisia). Asenapine was associated with higher incidence of sedation (18.6% vs 4.8%), dizziness (11.9% vs 3.8%), somnolence (8.8% vs 1.9%), fatigue (6.2% vs 1%), oral hypoaesthesia (5.2% vs 1%), dystonia in (4.1% vs 1.9%), and akathisia (2.6% vs 1.9%) compared with placebo. Additionally, asenapine patients reported a 1.6-kg

weight increase compared with 0.3-kg for placebo and 1.9 kg for olanzapine patients. Significant weight gain (7% or greater increase from baseline) occurred in 6%, 0% and 12.9% of patients in the asenapine, placebo, and olanzapine arms, respectively [4].

b) Adjunctive Therapy

1j) Adjunctive asenapine with either [lithium](#) or [valproate](#) significantly improved mania or mixed episodes associated with bipolar I disorder compared with placebo at week 3, in patients with an incomplete response to [lithium](#) or [valproate](#) monotherapy a randomized, double-blind, flexible-dose, 12-week study (n=326). Adult patients with or without psychotic features, who were partially responsive to at least 2 weeks of open-label [lithium](#) (dosed to trough levels of 0.6 to 1.2 mmol/L) or [valproate](#) (dosed to trough levels of 50 to 125 mcg/mL) monotherapy were randomized to double-blinded adjunctive therapy with sublingual asenapine (n=158; mean age, 39.6 years; 60.1% manic; baseline Young Mania Rating Scale (YMRS) score 28) or placebo (n=166; mean age, 39 years; 62% manic; baseline YMRS score 28.2). Asenapine was initiated at 5 mg twice daily and could be increased to 10 mg twice daily from day 2 onward as necessary. The mean dose of asenapine in all patients was 11.8 mg (11 mg in [valproate](#) group, 12.8 mg in [lithium](#) group), and the median duration of use was 42 days for asenapine and 30 days for placebo. Patients in the asenapine arm showed significant improvement in the least squares mean YMRS total score change from baseline to week 3 (primary endpoint; -10.3 vs -7.9; p=0.026) compared with placebo, which was also maintained at week 12 (secondary endpoint; -12.7 vs -9.3; p=0.0073). Secondary endpoints of YMRS remission rates and change from baseline on the Clinical Global Impression for [Bipolar Disorder](#) for mania and overall illness were also significantly improved in the asenapine arm compared with placebo. All other secondary endpoints including YMRS total score were not significantly different between groups. The most common adverse effects that occurred more frequently in patients treated with asenapine than in patients treated with placebo were sedation (13.3% vs 6%), somnolence (11.4% vs 4.2%), oral hypoesthesia (5.7% vs 0.6%), and increased weight (5.1% vs 0.6%). Patients that completed the core 12-week study (n=116) were eligible for enrollment into a blinded, placebo-controlled extension study for an additional 40 weeks. No conclusion about asenapine efficacy measures can be drawn at 52-weeks due to low number of patient completers (n=34) [5].

4.5.Bj [Schizophrenia](#), Acute treatment

FDA Labeled Indication

1j) 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](#)

2j) Summary:

Indicated for the acute treatment of [schizophrenia](#) in adults [1]

3) Adult:

a) Two 6-week, randomized, double-blind, placebo-controlled, fixed-dose studies demonstrated that asenapine was statistically superior to placebo in adult patients experiencing an acute episode of [schizophrenia](#). Patients meeting DSM-IV criteria for [schizophrenia](#) and having an acute exacerbation of their schizophrenic illness were randomized to asenapine or placebo and evaluated on the Positive and Negative Syndrome Scale (PANSS) to assess their symptoms of [schizophrenia](#). The primary efficacy endpoint was the change in PANSS score from baseline to endpoint. In trial 1, patients (n=174) were randomized to asenapine 5 milligrams (mg) twice daily or placebo. The PANSS score in patients receiving asenapine was statistically superior compared with patients receiving placebo. In trial 2, patients (n=448) were randomized to asenapine 10 mg twice a day, asenapine 5 mg twice a day, or placebo. The PANSS score in patients receiving asenapine 5 mg twice a day was statistically superior compared with patients receiving placebo. The PANSS score in patients receiving asenapine 10 mg twice a day showed no added benefit compared with patients receiving asenapine 5 mg twice a day and was not significantly different from placebo. A third trial of patients receiving asenapine, active control ([haloperidol](#), [risperidone](#), and [olanzapine](#)) or placebo found no difference between asenapine treatment and placebo; although an active control was found to be superior to placebo. No evidence of differential responsiveness was found based on age, gender, or race [2].

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