

DRUGDEX-EV 0729

MICROMEDEX

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PIMOZIDE

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

0.0] Overview

1] Class

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

Antipsychotic

2] Dosing Information

a) Adult

1) [Gilles de la Tourette's syndrome](#), in patients who have failed to adequately respond to standard treatment

a) initial, 1 to 2 mg a day ORALLY in divided doses; may increase dosage gradually every other day; usual maintenance dose is less than 10 mg/day or 0.2 mg/kg/day, whichever is smaller; doses greater than 10 mg/day or 0.2 mg/kg/day are not recommended [3]

b) Pediatric

1) effectiveness not established in children under 12 years of age for use in [Tourettes disorder](#); in children 2 to 12 years of age the safety profile was similar compared to older children[3]

2) use in pediatric patients for conditions other than [Tourettes disorder](#) is not recommended [3]

a) [Gilles de la Tourette's syndrome](#), in patients who have failed to adequately respond to standard treatment

1) (age 12 years and older) initial, 0.05 mg/kg/day ORALLY preferably taken once at bedtime; the dosage may be increased every third day up to a MAX dose of 0.2 mg/kg/day not to exceed 10 mg/day [3]

3] Contraindications

- a) Comatose states from any cause [1]
 - b) Concomitant use with [citalopram](#), escitalopram, or [sertraline](#) [1]
 - c) Concomitant use with CYP3A4 inhibitors ([nefazodone](#), [zileuton](#), [fluvoxamine](#)), the macrolide antibiotics (eg, [clarithromycin](#), [erythromycin](#), [azithromycin](#), [dirithromycin](#), or [troleandomycin](#)), the azole antifungals (eg, [itraconazole](#), [ketoconazole](#)), or the [protease](#) inhibitors (eg, [ritonavir](#), [saquinavir](#), [indinavir](#), or [nelfinavir](#)) [1]
 - d) Concomitant use with drugs that may cause motor and phonic tics (eg, [pemoline](#), [methylphenidate](#), or [amphetamines](#)) [1]
 - e) Concomitant use with QT-prolonging drugs (eg, [dofetilide](#), [sotalol](#), [quinidine](#), other Class Ia and III antiarrhythmics, [mesoridazine](#), [thioridazine](#), [chlorpromazine](#), [droperidol](#), [sparfloxacin](#), [gatifloxacin](#), [moxifloxacin](#), [halofantrine](#), [mefloquine](#), [pentamidine](#), [arsenic trioxide](#), [levomethadyl acetate](#), [dolasetron mesylate](#), [probucol](#), [tacrolimus](#), or [ziprasidone](#)) [1]
 - f) Concomitant use with strong CYP2D6 inhibitors (eg, [paroxetine](#)) [1]
 - g) Congenital [long QT syndrome](#) [1]
 - h) History of [cardiac arrhythmias](#) [1]
 - i) Hypersensitivity to [pimozide](#) [1]
 - j) Hypokalemia [1]
 - k) Hypomagnesemia [1]
 - l) Severe toxic CNS depression [1]
 - m) Simple tics or tics not associated with [Tourette syndrome](#) [1]
- 4) Serious Adverse Effects
- a) [Agranulocytosis](#)
 - b) [Cholestatic jaundice syndrome](#)
 - c) Death
 - d) Disorder of hematopoietic structure
 - e) [Drug-induced lupus erythematosus](#), Systemic
 - f) [Ineffective thermoregulation](#), [Heatstroke](#) or [hypothermia](#)
 - g) [Leukopenia](#)
 - h) [Neuroleptic malignant syndrome](#)
 - i) [Obstipation](#)
 - j) [Paralytic ileus](#)
 - k) [Priapism](#)

l)) Prolonged QT interval

m)) Seizure

n)) [Thrombocytopenia](#)

o)) [Torsades de pointes](#)

5)) Clinical Applications

a)) FDA Approved Indications

1)) [Gilles de la Tourette's syndrome](#), in patients who have failed to adequately respond to standard 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

[Pimozide](#)

C)) Physicochemical Properties

1)) Molecular Weight

a)) 461.56 [451]

2)) Solubility

a)) Systemic: Less than 0.01 mg per mL in water [452].

1.2) Storage and Stability

A)) Oral route

1)) Store Orap(R) tablets at controlled room temperature, 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) [43]. Dispense in a light resistant container.

1.3) Adult Dosage

1.3.1) Normal Dosage

1.3.1.A) Important Note

D) Perform CYP2D6 genotyping when the daily pimozide dose is greater than 4 mg in adults, or greater than 0.05 mg/kg in children [1].

D) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [2].

1.3.1.B) Chronic schizophrenia

1) Summary

a) Usual daily oral doses range from 2 to 12 milligrams and doses up to 20 mg have been used. Moderate doses of neuroleptic drugs, defined as between 165 and 375 milligram equivalent of chlorpromazine, were preferred in the maintenance therapy of chronic psychosis in a meta-analysis of 22 randomized control trials [22]. The association between dose and clinical effectiveness and side effects was assessed. At doses greater than 375 milligram equivalent of chlorpromazine, there was no incremental clinical improvement seen, and adverse reactions occurred at a significantly higher rate.

2) Effective doses in chronic schizophrenia have been 2 to 12 milligrams daily [12][23]; (Lapierre & Lavallee, 1975; Simms & Burnside, 1975)[24][11][25][10]. The optimal maintenance dose for patients previously maintained on other psychotic agents appears to be 6 mg daily [9]. In all studies, lower doses are initiated (2 mg daily) and increased based upon clinical response.

3) Evidence from clinical studies suggest that pimozide may be more effective in the treatment of autistic patients with chronic schizophrenia and associated emotional withdrawal, delusions and hallucinations, as opposed to the agitated and aggressive patients [10][9].

4) There is no relationship between types of previous antipsychotic medications and response to pimozide [9].

5) Pimozide was equally effective in doses of 3 or 8 milligrams daily in the treatment of schizophrenia; however, extrapyramidal symptoms were significantly higher in patients taking 8 milligram doses. The author recommends initial doses of 3 milligrams daily [26].

1.3.1.C) Gilles de la Tourette's syndrome, in patients who have failed to adequately respond to standard treatment

1) A slow and gradual introduction of pimozide is required to suppress tics; the dose should be carefully titrated to balance tic suppression with the untoward side effects of the drug. The recommended initial dose in adults for the suppression of motor and phonic tics associated with Tourettes disorder is 1 to 2 mg/day in divided doses, increasing thereafter every other day; most patients are maintained effectively on doses of less than 0.2 mg/kg/day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended [3].

2) Others recommend starting doses in both adults and children of 1 mg pimozide at bedtime, with dose increases of 1 mg every 5 to 7 days until symptoms are observed to decrease by at least 70%, or adverse effects occur without symptomatic benefit (or if symptoms decrease and adverse effects occur at the same time) [5].

1.3.1.D) Important Note

1) Sudden, unexpected deaths have occurred in patients receiving high doses of Orap(R) (ie, greater than 10 mg) [35].

1.3.1.E) Single Daily Dose

1) Due to the long half-life of pimozide, the drug may be administered once daily [9]. Other reports have indicated that 4 times the initial single daily dose was effective when administered weekly in chronic

[schizophrenia](#) (once weekly to a maximum of 60 mg). In one study, the average dose of [pimozide](#) weekly was 40 mg (range, 10 to 60 mg) [17].

1.3.3] Dosage in Hepatic Insufficiency

A) Reductions in dose should be considered in severe [hepatic insufficiency](#) since a large portion of the drug is metabolized in the liver [39].

1.3.4] Dosage in Geriatric Patients

A) An initial dosage of 1 mg/day is recommended in geriatric patients [38].

1.3.6] Dosage in Other Disease States

A) Drug discontinuation

1) When discontinuing therapy, [pimozide](#) should be withdrawn gradually over several weeks, to minimize symptoms of withdrawal [3].

B) Poor CYP2D6 Metabolizers

1) In adults who are poor CYP2D6 metabolizers, the daily dose should be limited to 4 mg per day. Dose increases should not be made sooner than 14-day intervals [3].

C) QT prolongation

1) If QT prolongation greater than an absolute limit of 0.52 seconds occurs in adults, or more than 25% above the patient's baseline, do not increase the dose any further and consider a lower dose [3].

D) Toxicity

1) If toxicity interferes slightly with functioning, dose reductions of 1 mg weekly are suggested. If toxicity is severe, the dose should be reduced by one half immediately; titration should be reinstituted at intervals ranging from 7 to 30 days after disappearance of severe adverse effects [5]

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Important Note

J) Perform CYP2D6 genotyping when the daily pimozide dose is greater than 4 mg in adults, or greater than 0.05 mg/kg in children [1].

J) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [2].

1.4.1.B] Oral route

1) The use of [pimozide](#) in pediatric patients for conditions other than [Tourettes disorder](#) is not recommended [3].

2) Doses of 1 to 2 mg daily have been effective in the treatment of schizophrenic and behavioral symptoms in children age 9 to 14 years [36]. Other data indicate the efficacy of 1 to 3 mg [pimozide](#) daily in adolescents 13 to 20 years of age with childhood or juvenile [schizophrenia](#) [37].

1.4.1.C] Gilles de la Tourette's syndrome, in patients who have failed to adequately respond to standard treatment

1J) The recommended initial [pimozide](#) dose in children age 12 years and older for the suppression of motor and phonic tics associated with [Tourettes disorder](#) is 0.05 mg/kg taken at bedtime. Every third day the dose may be increased to a maximum of 0.2 mg/kg but should not exceed 10 mg/day. Dose-response data concerning the effects of [pimozide](#) on tic manifestations in children younger than 12 years are unavailable [3].

2J) Others recommend starting doses in both adults and children of 1 mg [pimozide](#) at bedtime, with dose increases of 1 mg every 5 to 7 days until symptoms are observed to decrease by at least 70%, or adverse effects occur without symptomatic benefit (or if symptoms decrease and adverse effects occur at the same time) [5].

1.4.1.D) Important Note

1J) Sudden, unexpected deaths have occurred in patients receiving high doses of Orap(R) (ie, greater than 10 mg) [35].

1.4.1.E) Effectiveness of [pimozide](#) has not been established in children under 12 years of age for use in [Tourettes disorder](#); in children 2 to 12 years of age the safety profile was similar compared to older children [3].

1.4.1.F) The use of [pimozide](#) in pediatric patients for conditions other than [Tourettes disorder](#) is not recommended [3].

1.4.3] Dosage in [Hepatic Insufficiency](#)

AJ) Reductions in dose should be considered in severe [hepatic insufficiency](#) since a large portion of the drug is metabolized in the liver [39].

1.4.5] Dosage in Other Disease States

AJ) Drug discontinuation

1J) When discontinuing therapy, [pimozide](#) should be withdrawn gradually over several weeks, to minimize symptoms of withdrawal [3].

BJ) Poor CYP2D6 Metabolizers

1J) In children who are poor CYP2D6 metabolizers, the daily dose should be limited to 0.05 mg/kg per day. Dose increases should not be made sooner than 14-day intervals [3].

CJ) QT prolongation

1J) If QT prolongation greater than an absolute limit of 0.47 seconds occurs in children, or more than 25% above the patient's baseline, do not increase the dose any further and consider a lower dose [3].

DJ) Toxicity

1J) If toxicity interferes slightly with functioning, dose reductions of 1 mg weekly are suggested. If toxicity is severe, the dose should be reduced by one half immediately; titration should be reinstituted at intervals ranging from 7 to 30 days after disappearance of severe adverse effects [5]

2.0] Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

2.1] Onset and Duration

AJ) Onset

1)) Peak Response**a)) Schizophrenia:** 1 to 3 weeks [264]

1)) During a randomized, 28-day study of pimozide 3 mg and 8 mg in schizophrenic subjects, peak response was seen after 1 to 3 weeks of treatment [264].

2.2) Drug Concentration Levels**A)) Peak Concentration****1))** Oral, single-dose, 2 mg, children: 7.2 nanograms/mL [265]

a)) Following a single 2 mg oral dose of pimozide in children with Tourette's syndrome, peak plasma concentrations of 7.2 nanograms/mL were achieved in approximately 7 hours [265].

2)) Oral, single dose, adults: 4 nanograms/mL (6 mg); 16 nanograms/mL (24 mg) [266].

a)) Peak plasma levels following single oral doses of 6 mg and 24 mg in adults with schizophrenia were 4 nanograms/mL and 16 nanograms/mL at 6 hours, respectively [266].

3)) Oral, multiple-dose, 6 mg, adults: 10 nanograms/mL [266]

a)) Following multiple doses of 6 mg once daily for 4 days in adults with schizophrenia, peak plasma concentrations were 4, 5, 8, and 10 nanograms/mL on each successive day [266].

B)) Time to Peak Concentration**1))** Oral: 6 to 8 hours [3][265][266].

a)) Peak plasma levels occur 6 to 8 hours (range 4 to 12 hours) after pimozide administration [3].

b)) Peak plasma levels following single oral doses of 6 mg and 24 mg in adults with schizophrenia were 4 nanograms/mL and 16 nanograms/mL at 6 hours, respectively [266].

c)) Following a single 2 mg oral dose of pimozide in children with Tourette's syndrome, peak plasma concentrations of 7.2 nanograms/mL were achieved in approximately 7 hours [265].

2.3) ADME**2.3.1) Absorption****A)) Bioavailability****1))** More than 50% [3]

a)) More than 50% of an oral dose of pimozide is absorbed following oral administration [3].

B)) Effects of Food**1))** Unknown [3]

- a) The effects of food on the pharmacokinetics of [pimozide](#) are not known [3].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

- 1) Liver: extensive, primarily via CYP3A4 [3][267][268].

a) [Pimozide](#) is metabolized via N-dealkylation, catalyzed primarily by CYP3A4 and to a lesser extent by CYP1A2 and CYP2D6 isoenzymes [3][267][268].

b) CYP2D6 [genotyping](#) is recommended in pediatric patients when daily dose exceeds 0.05 mg/kg/day and in adult patients when daily dose exceeds 4 mg/day. Dosage adjustment is recommended in known poor CYP2D6 metabolizers [3].

B) Metabolites

- 1) 4, 4-bis-(4-fluorophenyl) butyric acid (major): unknown [3][268]

a) The antipsychotic activity of this major metabolite is unknown [3].

- 2) 1-(4-piperidyl)-2-benzimidazolinone (major): unknown [3][268]

a) The antipsychotic activity of this major metabolite is unknown [3].

2.3.4] Excretion

A) Kidney

- 1) Renal Excretion (%)

a) major route [3]

1) Renal excretion is the major route of elimination of pimozide and its metabolites [3][265]

2) Excreted drug is 1% unchanged drug and two-thirds the 4-bis-(4-fluorophenyl) butyric acid metabolite [268].

2.3.5] Elimination Half-life

A) Parent Compound

- 1) 55 to 66 hours [3][265]

a) The mean elimination half-life of [pimozide](#) in schizophrenic patients is approximately 55 hours [3].

b) An elimination half-life of 66 hours was reported in children with [Tourette's syndrome](#) following a single 2 mg oral dose of [pimozide](#) [265].

3.0] Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.1] Contraindications

- A) Comatose states from any cause [1]
- B) Concomitant use with [citalopram](#), escitalopram, or [sertraline](#) [1]
- C) Concomitant use with CYP3A4 inhibitors ([nefazodone](#), [zileuton](#), [fluvoxamine](#)), the macrolide antibiotics (eg, [clarithromycin](#), [erythromycin](#), [azithromycin](#), [dirithromycin](#), or [troleandomycin](#)), the azole antifungals (eg, [itraconazole](#), [ketoconazole](#)), or the [protease](#) inhibitors (eg, [ritonavir](#), [saquinavir](#), [indinavir](#), or [nelfinavir](#)) [1]
- D) Concomitant use with drugs that may cause motor and phonic tics (eg, [pemoline](#), [methylphenidate](#), or [amphetamines](#)) [1]
- E) Concomitant use with QT-prolonging drugs (eg, [dofetilide](#), [sotalol](#), [quinidine](#), other Class Ia and III antiarrhythmics, [mesoridazine](#), [thioridazine](#), [chlorpromazine](#), [droperidol](#), [sparfloxacin](#), [gatifloxacin](#), [moxifloxacin](#), [halofantrine](#), [mefloquine](#), [pentamidine](#), [arsenic trioxide](#), [levomethadyl acetate](#), [dolasetron](#) mesylate, [probutol](#), [tacrolimus](#), or [ziprasidone](#)) [1]
- F) Concomitant use with strong CYP2D6 inhibitors (eg, [paroxetine](#)) [1]
- G) Congenital [long QT syndrome](#) [1]
- H) History of [cardiac arrhythmias](#) [1]
- I) Hypersensitivity to [pimozide](#) [1]
- J) Hypokalemia [1]
- K) Hypomagnesemia [1]
- L) Severe toxic CNS depression [1]
- M) Simple tics or tics not associated with [Tourette syndrome](#) [1]

3.2] Precautions

- A) Beers Criteria: Avoid use in older adults for behavioral problems of [dementia](#) or [delirium](#) (unless nonpharmacological measures fail and the patient is a threat to self or others) due to increased risk of cerebrovascular accident and mortality. Avoid use in patients with [Parkinson Disease](#) as symptoms may worsen, and in patients with a history of falls or fractures (unless safer alternatives are not available), or cognitive impairment due to risk of adverse CNS effects, syncope, ataxia, and impaired psychomotor performance. If prescribed, SIADH or [hyponatremia](#) may occur; monitoring recommended when starting or changing doses [2].
- B) Cardiovascular: Sudden and unexpected death has been reported with dosages in the range of 1 mg/kg, potentially due to [ventricular arrhythmia](#) secondary to QT prolongation; monitoring recommended [1]
- C) Concomitant use: Concomitant ingestion of grapefruit juice should be avoided [1]
- D) Hematologic: [Agranulocytosis](#), [leukopenia](#), and [neutropenia](#) have been reported , with an increased risk with preexisting low WBC or history of drug-induced [leukopenia](#) or [neutropenia](#); monitoring recommended and discontinuation may be necessary [1]
- E) Hepatic: Risk of toxicity in patients with [hepatic impairment](#) [1]
- F) Neurologic: Potentially fatal [neuroleptic malignant syndrome](#) has been reported with antipsychotic drugs; immediately discontinue if occurs [1]
- G) Neurologic: [Tardive dyskinesia](#) that is potentially irreversible may occur, with an increased risk in elderly patients, especially women, and with increased duration of treatment or increased total cumulative antipsychotic

drug doses; administer the smallest dose for the shortest duration of treatment and consider discontinuation if symptoms occur [1]

H)) Neurologic: May lower the seizure threshold in patients with history of seizure, those receiving anticonvulsant medication, or patients with EEG abnormalities [1]

I)) Neurologic: Anticholinergic side effects may occur affecting conditions aggravated by anticholinergic activity [1]

J)) Neurologic: [Hyperpyrexia](#) has been reported with antipsychotic drugs [1]

K)) Renal: Risk of toxicity in patients with [renal impairment](#) [1]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Cardiovascular finding

1)) Sudden cardiac death, prolongation of the QT interval with possible [ventricular arrhythmias](#), and hypotension are described with the administration of [pimozide](#).

3.3.1.B] Hypotension

1)) Summary

a)) Isolated reports of hypotension have been reported during treatment with [pimozide](#) [40][41][42].

3.3.1.C] Prolonged QT interval

1)) During experimental studies of [pimozide](#) for conditions other than [Tourette's syndrome](#), sudden, unexpected deaths occurred. [Pimozide](#) dosages were approximately 1 mg/kg. It is speculated that prolongation of the QT interval predisposed patients to [ventricular arrhythmia](#). The manufacturer recommends performing an ECG before initiation of [pimozide](#) therapy and periodically thereafter, especially during periods of dose adjustment [43].

2)) ECG changes seen during clinical trials in [Tourette's syndrome](#) and [schizophrenia](#) patients include prolongation of the QT interval, flattening, notching, and inversion of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 mg/day [43].

3.3.1.D] Sudden cardiac death

1)) Summary

a)) Sudden death is described with administration of [pimozide](#). The mechanism may be due to PROLONGED QT INTERVAL and the development of [VENTRICULAR ARRHYTHMIAS](#) [43][44][45][40][46].

2)) LITERATURE REPORTS

a)) During experimental studies of [pimozide](#) for conditions other than [Tourette's syndrome](#), sudden, unexpected deaths occurred. [Pimozide](#) dosages were approximately 1 milligram/kilogram (mg/kg). It is speculated that prolongation of the QT interval predisposed patients to [ventricular arrhythmia](#). The manufacturer recommends performing an [electrocardiogram](#) (ECG) before initiation of [pimozide](#) therapy and periodically thereafter, especially during periods of dose adjustment [43].

b)) [Electrocardiogram](#) (ECG) changes seen during clinical trials in [Tourette's syndrome](#) and [schizophrenia](#) patients include prolongation of the QT interval, flattening, notching, and inversion

of the T wave, and the appearance of U waves. Sudden, unexpected deaths have occurred at doses greater than 20 milligrams/day [43].

c) The manufacturer of [pimozide](#) has reported sudden, unexpected deaths in some patients taking doses greater than 10 milligrams (mg). Deaths are due to ventricular [dysrhythmia](#) probably as a result of prolongation of the QT interval. Drug interactions with drugs inhibiting metabolism of [pimozide](#) and resulting in increased plasma concentrations could result in QT prolongation (Anon, 1999).

d) An association with sudden death in schizophrenic patients has been postulated from doses in the 1 milligram/kilogram (mg/kg) range. The mechanism may be from prolongation of the QT interval [45][44].

e) About 25% of patients taking therapeutic dosages of [pimozide](#) have prolonged QT intervals similar to those caused by the phenothiazines [45].

f) Most studies have reported no significant effect of [pimozide](#) therapy, in high or low doses, on the [electrocardiogram](#) [40].

g) One report of T WAVE CHANGES on [electrocardiogram](#) has been reported with [pimozide](#) therapy; however, a definite cause/effect relationship was not established [46].

3.3.2] Dermatologic Effects

3.3.2.A] Acne

1) Summary

a) CASE REPORT - One case of [ACNE VULGARIS](#) has been reported possibly in association with [pimozide](#) administration [42].

3.3.2.B] Edema of face

1) Summary

a) Facial edema has been reported with administration of [pimozide](#) [59].

3.3.2.C] Rash

1) Summary

a) ERYTHEMATOUS SKIN RASHES occurred infrequently during [pimozide](#) administration [40].

3.3.2.D] Skin finding

1) Skin rashes, acne, and facial edema are described with the administration of [pimozide](#).

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] [Hyperprolactinemia](#)

1) Overview

- a) Antipsychotic-induced [hyperprolactinemia](#) was reported in 65.6%, 45.1%, and 42.4% of women of childbearing potential, postmenopausal women, and men, respectively, in an open-label, clinical trial of patients treated with first-generation antipsychotics or [risperidone](#) at average doses of 4.2 to 5.2 mg/day. Compared to baseline, prolactin levels were significantly elevated (p less than 0.05) following use of first-generation antipsychotics (ie, [chlorpromazine](#), [droperidol](#), flupenthixol, [fluphenazine](#), [haloperidol](#), [paliperidone](#), perazine, [perphenazine](#), [pimozide](#), [trifluoperazine](#), and zuclopenthixol) or [risperidone](#) in several clinical trials of patients with [schizophrenia](#). Younger patients and women of childbearing potential have a greater risk for [hyperprolactinemia](#) following treatment with higher doses of these antipsychotics. [Hyperprolactinemia](#) may potentially result in menstrual disturbances, sexual dysfunction, [bone mineral density](#) (ie, [osteopenia](#) and [osteoporosis](#)), and breast and [pituitary tumors](#) [62].
- 2) [Hyperprolactinemia](#) has been reported with antipsychotic drugs; the elevation in prolactin persists during chronic administration [61]. [Pimozide](#) is associated with increased serum prolactin [63].
- 3) The effect of [pimozide](#) on hypothalamo-pituitary functions was studied in 13 children with behavior disorders. [Pimozide](#) was associated with an increase in serum prolactin levels. No significant influence on growth hormone or cortisol secretion was induced by [hypoglycemia](#). [Serum thyroxine](#) and triiodothyronine were not influenced by [pimozide](#) [64].

a) Management

- 1) Appropriate drug selection, monitoring and management are all important when prescribing antipsychotics that have the potential for inducing [hyperprolactinemia](#). Prior to treatment with an antipsychotic, question patients regarding changes in libido or [galactorrhea](#). Female patients should be assessed for menstrual abnormalities and male patients, for erectile or ejaculatory dysfunction. In the event that any of these symptoms are present, consider obtaining baseline prolactin levels. Patients should be informed of the potential for sexual dysfunction with antipsychotic use. Several weeks after an antipsychotic is initiated, obtain a prolactin level measurement. In cases where the patient experiences troublesome adverse effects related to elevated prolactin levels and discontinuing the antipsychotic is not an option, treatment with a [dopamine](#) agonist (eg, [bromocriptine](#) or [cabergoline](#)) should be considered [62].

3.3.3.B) [Hyponatremia](#)

- 1) [Hyponatremia](#) has been reported during post-marketing use of [pimozide](#); causality cannot be established [61].

3.3.3.C) [Weight gain](#)

- 1) Weight gain has been reported in patients treated with [pimozide](#) for conditions other than [Tourette's disorder](#) [61].

3.3.3.D) [Weight loss](#)

- 1) Weight loss has been reported in patients treated with [pimozide](#) for conditions other than [Tourette's disorder](#) [61].

3.3.4) [Gastrointestinal Effects](#)

3.3.4.A) [Gastrointestinal tract finding](#)

1) Summary

a) **Pimozide** has infrequently been associated with gastrointestinal side effects including anorexia, NAUSEA, ABDOMINAL PAIN, DIARRHEA, and CONSTIPATION [65][40][49].

2) Nausea, abdominal pain, diarrhea, constipation, and anorexia are associated with the administration of **pimozide**.

3.3.4.B) Loss of appetite**1) Summary**

a) Significant weight loss (average 5.4 kilograms) was reported in all patients receiving **pimozide** for maintenance treatment of **chronic schizophrenia** [54].

3.3.6) Hepatic Effects**3.3.6.A) Hepatotoxicity**

1) Transient increases in **alkaline phosphatase** have occurred during **pimozide** treatment; however, a cause/effect relationship has not been established. No cases of hepatic damage have been reported [46].

3.3.8) Musculoskeletal Effects**3.3.8.A) Decreased bone mineral density****1) General Information**

a) Most likely due to persistent **hyperprolactinemia** during use [71]

2) Adult Clinical Trials

a) **Schizophrenia** or **schizoaffective disorder**: Regardless of treatment duration, 23% of women and 31% of men receiving **risperidone** or a conventional antipsychotic, including **pimozide**, had low **bone mineral density**; while 61% of women and 43% of men had **hyperprolactinemia**. After controlling for age, low **bone mineral density** was associated with **hyperprolactinemia** in men, but not in women [71]

3.3.9) Neurologic Effects**3.3.9.A) Extrapyramidal disease****1) Summary**

a) Extrapyramidal reactions to **pimozide** are the most frequent side effects of the drug, primarily **TARDIVE DYSKINESIA**, **AKATHISIA**, **DYSTONIC REACTIONS**, **TREMORS** and **PARKINSONIAN SYMPTOMS**, occurring in up to 15% of patients treated. Extrapyramidal reactions are generally dose- related in most patients and have been reversed by dose reduction in the majority [43][40].

2) LITERATURE REPORTS

a) **Tardive dyskinesia** (TD) due to **pimozide** seems to be rare, occurring in some patients on long-term therapy or after drug therapy has been discontinued. The risk may be greater for elderly patients on high-dose therapy [43].

b)) A 6-year-old autistic boy developed repeated episodes of ACUTE DYSTONIC REACTION while receiving pimozone and subsequently thioridazine. Acute dystonic reactions occur within the first few days of neuroleptic administration and they are well controlled with diphenhydramine in children [50].

c)) Tardive dyskinesia appeared in a 17-year-old boy following withdrawal from a combination of pimozone and thioridazine. The CHOREODYSKINETIC MOVEMENT of the limbs and the trunk cleared with anticholinergic drugs but were dramatically worsened by dopaminergic receptor blockers [51].

d)) A case is reported of a 16-year-old female treated with pimozone 4 milligrams/day (mg/day) for 1 day, the dose increased to 6 mg/day for 1 day. She developed neck stiffness and OCULOGYRIC CRISIS, which resolved with benztropine 2 milligrams intramuscularly. The dose was reduced to 4 milligrams/day (mg/day) on day 3 but later in the day she suffered a tonic-clonic seizure. Pimozone was discontinued and no further seizures occurred [52].

e)) Some evidence indicates that pimozone exerts more prolific extrapyramidal effects than haloperidol [53].

f)) Extrapyramidal reactions respond readily to anticholinergic agents. Tardive dyskinesia was reported in 35% of patients receiving pimozone in one study [54].

g)) Pimozone has been mentioned as the causal agent in tardive dyskinesia (TD) in one review [55].

h)) A single case of a 50-year-old alcoholic with late onset extrapyramidal side effects thought related to pimozone and alcohol withdrawal or alcohol intake was reported [56].

i)) A severe dystonic reaction requiring discontinuance of pimozone and treatment with benztropine and diazepam was reported in a patient taking 4 milligrams/day for approximately 6 weeks [57].

j)) Sixteen patients were given pimozone doses up to 60 milligrams/day for 28 days with few side effects. Most notable were mild extrapyramidal effects (tremors and PERIORAL DYSKINESIAS) which responded to antiparkinsonian medication. Side effects were never prominent enough to require discontinuance of therapy (Shopin & Selzer, 1977).

k)) Extrapyramidal effects may occur with therapeutic use. Extrapyramidal effects appeared only in the pimozone group in a placebo-controlled trial [46].

3.3.9.B] Neuroleptic malignant syndrome

1)) Summary

a)) Neuroleptic malignant syndrome has been reported after pimozone administration [43].

2)) Incidence: rare

3.3.9.C] Neurological finding

1)) Summary

a)) AKATHISIA, SEDATION, and DROWSINESS, are described with the administration of pimozone [43][47][48][40][49][48][42].

2) Excitement, insomnia, sedation, tinnitus, headache, extrapyramidal effects, dystonic reactions and seizures are described with the administration of [pimozide](#).

3) LITERATURE REPORTS

a) Drowsiness was reported in one 35-year-old patient receiving [pimozide](#) [48].

b) Infrequently, [pimozide](#) has been associated with excitement, insomnia, anxiety, agitation, tinnitus, and headache [40][49][48][42].

3.3.9.D] [Parkinsonism](#)

1) Summary

a) Contrary to common belief, the results of a retrospective cohort study suggest that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered [60].

2) LITERATURE REPORTS

a) The results of a cohort study indicate that high-dose atypical antipsychotic therapy carries a similar risk for the development of [parkinsonism](#) as does typical antipsychotic therapy. In a population-based, retrospective cohort study, adults (aged 66 years and older) with evidence of [dementia](#) were followed for up to 1 year for the development of [parkinsonism](#) symptoms associated with typical or atypical antipsychotic use. As compared with older adults receiving atypical antipsychotic therapy (ie, [olanzapine](#), [risperidone](#), [quetiapine](#)), incident [parkinsonism](#) was 30% more likely to occur in those taking typical antipsychotics (ie, [chlorpromazine](#), [haloperidol](#), [perphenazine](#)) (adjusted HR, 1.3; 95% CI, 1.04 to 1.58), and 60% less likely to occur in patient who did not receive either therapy (HR, 0.4; 95% CI, 0.29 to 0.43). Older adults using higher potency typical antipsychotics had almost a 50% greater risk of experiencing [parkinsonism](#) as compared with patients prescribed atypical antipsychotics (all were considered lower potency) (HR, 1.44; 95% CI, 1.13 to 1.84); however, in patients receiving lower potency typical antipsychotics, the risk of developing [parkinsonism](#) was no different from that in adults taking atypical antipsychotics (HR, 0.75; 95% CI, 0.48 to 1.15). In addition, a positive dose-related relationship was observed between the occurrence of incident [parkinsonism](#) and the use of atypical antipsychotics. The risk for developing [parkinsonism](#) was more than twice as great in patients using a high-dose atypical antipsychotic agent as compared with those prescribed a low-dose atypical antipsychotic agent (HR, 2.07; 95% CI, 1.42 to 3.02). Furthermore, patients taking a typical antipsychotic were found to have a similar risk for the development of [parkinsonism](#) as patients receiving high-dose atypical antipsychotic therapy (p=ns). The authors conclude that atypical antipsychotics may not be safer than typical antipsychotics when dose and potency are considered [60].

3.3.9.E] [Seizure](#)

1) Summary

a) Seizures are described with the administration of [pimozide](#) [52][58][40][59].

2) Incidence: rare

3) LITERATURE REPORTS

a) A case report described a GRAND MAL SEIZURE in a 16-year-old girl during treatment of [anorexia nervosa](#) with [pimozide](#). The seizure occurred after receiving 4 to 6 milligrams/day for 3 days. On the second day of treatment, the patient developed an [oculogyric crisis](#) which responded to [benztropine](#) [52].

- b)) Pimozide may lower the seizure threshold in both epileptic and non-epileptic patients [40].
- c)) Seizure activity has been reported during pimozide therapy. It is unclear if pimozide possesses epileptogenic potential, but the drug should be used cautiously in epileptic patients [58].
- d)) Seizures are described in three patients with no prior history of seizures and no exposure to epileptogenic drugs. All had been given pimozide and all had the dosage reduced or stopped prior to the seizures. The interval between the dosage change and the onset of seizures was 13 to 31 days. The dose given was not stated [58].
- e)) 13.3% (n=30) of patients given pimozide developed slight tremor and two of these had slight rigidity on doses increasing to 9 milligrams per day [59].

3.3.10] Ophthalmic Effects

3.3.10.A] Blurred vision

1)) Summary

- a)) Blurred vision has occurred infrequently with pimozide therapy [68][65].

3.3.10.B] Edema of eyelid

1)) Summary

- a)) Blurred vision has occurred infrequently with pimozide therapy [68][65].

3.3.10.C] Eye / vision finding

- 1)) Blurred vision, edema of the eyelids (blepharedema), pupillary paralysis, OCULOGYRIC CRISIS, and retinal pigmentation are described with the administration of pimozide [67].

3.3.10.D] Pupillary paralysis

1)) Summary

- a)) Pupillary paralysis was reported in a 24-year-old female following several weeks of therapy with pimozide 6 to 8 milligrams daily for schizophrenia [69].

2)) LITERATURE REPORTS

- a)) A patient developed parkinsonian tremor of the hands and legs and poor visual acuity followed by paralysis of the ciliary muscle of the eyes with fixed dilated pupils and paralysis of accommodation after pimozide administration. Benztropine 2 milligrams three times a day was administered resulting in alleviation of parkinsonian symptoms. The dose of pimozide was reduced to 2 milligrams daily and orphenadrine 50 milligrams (mg) three times a day was substituted for benztropine. Pupillary response gradually returned to normal over a period of 2 weeks [69].

3.3.10.E] Retinal pigment deposits

1)) Summary

- a)) CASE REPORT - A single case of retinal pigmentation was reported in a patient on long-term fluphenazine who also received pimozide and haloperidol [70]. Other authors indicated no changes in ocular pigmentation with pimozide use as noted by slit-lamp examination [40].

3.3.12] Psychiatric Effects

3.3.12.A] Psychiatric sign or symptom

1) Summary

a) DEPRESSION, PHOBIAS and ANXIETY are described with the administration of [pimozide](#) [43][47][48][40][49][48][42].

2) Depression, anxiety, agitation and phobias are described with the administration of [pimozide](#).

3) LITERATURE REPORTS

a) Four of 7 men being treated for [stuttering](#) with [pimozide](#) developed depression as measured on the [Beck Depression Inventory](#) [47]. [Pimozide](#) was started at 2 milligrams (mg)/day and increased, as tolerated, to 10 milligrams (mg). Three subjects became euthymic at 7 to 15 days after discontinuation. One subject was successfully treated with an antidepressant. Also, of these 4 subjects, 1 developed [akathisia](#) and 3 developed mild parkinsonian symptoms.

b) One of the main advantages of [pimozide](#) over other neuroleptics is its low propensity to produce sedation and drowsiness. Very few clinical studies have reported sedation as a significant side effect. Infrequently, [pimozide](#) has been associated with excitement, insomnia, anxiety, agitation, tinnitus, and headache [40][49][48][42].

c) [SCHOOL PHOBIA](#) induced by [pimozide](#) was reported in an 11- year-old boy being treated for [Tourette syndrome](#). This type of pimozide-induced SEPARATION ANXIETY may be unique to patients with [Tourette syndrome](#) [72].

d) Several patients developed dose-related [dysphoria](#) or depression with administration of [pimozide](#) (Bruun, 1988). In every case a "threshold dose" could be identified above which the patient complained of [dysphoria](#).

e) Depression, and [dysphoria](#) are described as frequent adverse effects of [pimozide](#) [73].

3.3.13] Renal Effects

3.3.13.A] Nocturnal enuresis

1) Summary

a) CASE REPORT - Nocturnal [enuresis](#) has been reported in one patient (9-year-old male) with [Gilles de la Tourette syndrome](#) during the 18 months of treatment with [pimozide](#) 1 to 4 milligrams at bedtime (specific onset not described). [Enuresis](#) was controlled by administering [pimozide](#) as a single dose in the morning instead of the evening [66].

3.3.13.B] Urinary incontinence

1) Summary

a) CASE REPORT ? Shapiro reported on a 9 year old with [Tourette's syndrome](#) treated with [pimozide](#) (3 milligrams at night) and [methylphenidate](#) (5 milligrams twice daily) for 1 1/2 years. Although the child had a history of night time [enuresis](#) prior to using the drug, when given the drug at bedtime control was lost. [Methylphenidate](#) was discontinued without effect on [enuresis](#). When [pimozide](#) was stopped or when given in the morning, night time [enuresis](#) did not occur [66].

3.3.13.C] Urogenital finding

1]) Nocturnal [enuresis](#), [urinary incontinence](#), and sexual dysfunction are described with the administration of [pimozide](#).

3.3.14] Reproductive Effects

3.3.14.A] Sexual dysfunction

1]) Summary

a]) IMPOTENCE was reported in a 37-year-old male following 2 months of treatment with [pimozide](#) 60 milligrams daily for [psychosis](#). The patient could not maintain an erection and this persisted for one month. [Pimozide](#) was discontinued and erection was possible 2 weeks later. However, [psychosis](#) recurred resulting in readministration of [pimozide](#). The patient exhibited EJACULATION DISTURBANCES when the dose was increased gradually from 4 to 12 milligrams daily. With doses of 16 milligrams daily the patient again became impotent [74].

3.3.16] Other

3.3.16.A] Death

1]) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with [dementia](#). Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the [dementia](#) cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined [75].

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

of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with [risperidone](#), the mortality ratio associated with [haloperidol](#) was 2.14 (95% CI, 1.86 to 2.45) and [loxapine](#) was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with [olanzapine](#). The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study [76].

3J) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: RR, 1.37; 95% CI, 1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI, 1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI, 1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI, 1.14 to 1.41). In addition, the adjusted risks of death observed in patients with [dementia](#) (RR, 1.29; 95% CI, 1.15 to 1.45), without [dementia](#) (RR, 1.45; 95% CI, 1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI, 1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI, 1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI, 1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided [77].

3.3.16.BJ Fever

1J) Summary

aJ) Severe [HYPERPYREXIA](#) requiring discontinuance of therapy was reported in one of twenty patients receiving [pimozide](#) [46].

3.4J Teratogenicity/Effects in Pregnancy/Breastfeeding

AJ) Teratogenicity/Effects in Pregnancy

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

aJ) 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](#).

2J) Australian Drug Evaluation Committee's (ADEC) Category: B1

aJ) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3J) Crosses Placenta: Unknown

4) Clinical Management

a) There are no adequate and well-controlled studies of [pimozide](#) use during pregnancy. However, third-trimester antipsychotic drug exposure has been associated with extrapyramidal and/or withdrawal symptoms in neonates. Therefore, [pimozide](#) should be used during pregnancy only if the maternal benefit justifies the fetal risk [167].

5) Literature Reports

a) There are no adequate and well-controlled studies of [pimozide](#) use in pregnant women. Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care [167].

b) Although studies conducted in rats and rabbits have shown that [pimozide](#) is not teratogenic, oral doses up to 8 times the maximum human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects may be caused by implantation inhibition or delay and are similarly observed in rodents administered other antipsychotic drugs. Maternal toxicity, mortality, decreased weight, and embryotoxicity (eg, increased resorptions) were dose-related in the rabbit studies [167].

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) There are insufficient data to determine if [pimozide](#) is excreted in human breast milk. As many drugs are excreted in breast milk and there is potential for serious adverse effects ([tumorigenicity](#), unknown cardiovascular effects) to the nursing infant, a decision should be made to discontinue breastfeeding or discontinue [pimozide](#) [167].

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] Abiraterone

1) Interaction Effect: increased plasma concentrations of CYP2D6 substrate

2) Summary: Coadministration of abiraterone (a CYP2D6 inhibitor) with a CYP2D6 substrate may result in increased plasma concentrations of the CYP2D6 substrate. When abiraterone (1000 mg/day) and [prednisone](#) (5 mg twice daily) were coadministered with the CYP2D6 substrate [dextromethorphan](#) (30 mg), the [dextromethorphan](#) C_{max} and AUC were increased 2.8-fold and 2.9-fold, respectively. If an

alternative to the CYP2D6 substrate cannot be used, use caution and consider reducing the dose of the CYP2D6 substrate as necessary during coadministration[119].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of abiraterone, a CYP2D6 inhibitor, with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate. If an alternative to the CYP2D6 substrate cannot be used, use caution and consider a dose reduction of the CYP2D6 substrate as indicated during coadministration[119].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by abiraterone

3.5.1.B] Alefacept

1) Interaction Effect: decreased pimozone plasma concentrations

2) Summary: The concomitant use of pimozone (a CYP3A substrate with a narrow therapeutic range) [3] with alefacept may result in decreased pimozone plasma concentrations. Alefacept inhibits cytokine release, which in turn could normalize the formation of CYP450 enzymes. If concomitant use is required, the dose of pimozone may need to be increased. When alefacept is discontinued, monitor for pimozone toxicity and adjust the dose as needed [147].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of alefacept with pimozone may decrease pimozone plasma concentrations. If concomitant use is required, the dose of pimozone may need to be increased. When alefacept is discontinued, monitor for pimozone toxicity and adjust the dose as needed[147].

7) Probable Mechanism: normalized CYP3A-mediated pimozone metabolism by alefacept

3.5.1.C] Alfuzosin

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

2) Summary: The concomitant use of pimozone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of pimozone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.D] Amifampridine

1) Interaction Effect: increased risk of QT-interval prolongation and increased or decreased exposure of drugs with a narrow therapeutic index

2) Summary: The concomitant use of amifampridine with drugs that prolong the QT interval and that have a narrow therapeutic index is contraindicated. Coadministration may increase the risk of ventricular arrhythmias. There are no data on the effects of amifampridine on the metabolism or active secretion of other drugs[100].

3) Severity: contraindicated

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amifampridine with drugs that prolong the QT interval and that have a narrow therapeutic index is contraindicated. Coadministration may increase the risk of [ventricular arrhythmias](#). There are no data on the effects of amifampridine on the metabolism or active secretion of other drugs[100].
- 7) Probable Mechanism: additive QT-interval prolongation; unknown (drugs with a narrow therapeutic index)

3.5.1.E] Amiodarone

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

3.5.1.F] Amisulpride

- 1) Interaction Effect: increased risk of [torsades de pointes](#)
- 2) Summary: The concomitant use of amisulpride with other agents that may induce [torsade de pointes](#) is contraindicated. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of [torsade de pointes](#)[131].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of amisulpride with other agents that may induce [torsade de pointes](#) is contraindicated. Because amisulpride by itself prolongs the QT interval in a dose-dependent manner, coadministration with another medication that prolongs the QT interval increases the risk of [torsade de pointes](#)[131].
- 7) Probable Mechanism: additive QT prolongation

3.5.1.G] Amitriptyline

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

3.5.1.H] Amprenavir

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT interval prolongation, **torsades de pointes**, **cardiac arrest**)
- 2) Summary: Amprenavir is an inhibitor of the isoenzyme cytochrome P450 3A; concomitant use with **pimozide** may result in inhibition of **pimozide** metabolism. Elevated **pimozide** serum concentrations have been associated with an increased risk of **cardiotoxicity**. The concurrent administration of **amprenavir** and **pimozide** is contraindicated[174].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of **amprenavir** and **pimozide** is contraindicated.
- 7) Probable Mechanism: increased **pimozide** serum concentrations due to inhibition of cytochrome P450 3A-mediated **pimozide** metabolism

3.5.1.I] Anagrelide

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

3.5.1.J] Apomorphine

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

3.5.1.K] Aprepitant

- 1) Interaction Effect: an increase in **pimozide** plasma concentrations
- 2) Summary: Concurrent use of **aprepitant** (a CYP3A4 inhibitor) and **pimozide** (a CYP3A4 substrate) is contraindicated as increased levels of **pimozide** may result in QT interval prolongation[209].
- 3) Severity: contraindicated
- 4) Onset: unspecified

- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [aprepitant](#) (a CYP3A4 inhibitor) and [pimozide](#) (a CYP3A4 substrate) is contraindicated as increased levels of [pimozide](#) may result in QT interval prolongation[209].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [pimozide](#) by [aprepitant](#)

3.5.1.L] [Aripiprazole](#)

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

3.5.1.M] [Arsenic Trioxide](#)

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

3.5.1.N] [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 [pimozide](#) with other drugs that prolong the QT interval, including artemether/lumefantrine, is contraindicated[3]. Coadministration of lumefantrine, a CYP2D6 inhibitor, with [pimozide](#), a CYP2D6 substrate, may result in increased [pimozide](#) plasma levels, further increasing the risk of QT-interval prolongation. Caution is also 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) [234].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [pimozide](#) with other drugs that prolong the QT interval, including artemether/lumefantrine, is contraindicated due to the potential for additive effects on QT-interval prolongation[3]. 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) [234].

7J) Probable Mechanism: additive effects on QT-interval prolongation; inhibition of CYP2D6-mediated metabolism of [pimozide](#)

3.5.1.O] Asenapine

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.P] Astemizole

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.Q] Atazanavir

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.R] Azithromycin

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

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

3.5.1.S) Bedaquiline

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

3.5.1.T) Belladonna

- 1)) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
- 2)) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with [pimozide](#). Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots[171]. Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with [pimozide](#) is unknown. Caution is advised.
- 3)) Severity: minor
- 4)) Onset: rapid
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, [tachycardia](#), decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, [paralytic ileus](#), confusion, [psychoses](#), agitation, delusions, [delirium](#), and paranoia may be encountered as well as [tachycardia](#), [dysrhythmia](#), and [hypertension](#). In severe cases, immediate medical attention should be obtained.
- 7)) Probable Mechanism: additive anticholinergic effect

3.5.1.U) Belladonna Alkaloids

- 1)) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)
- 2)) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with [pimozide](#). Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots[171]. Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with [pimozide](#) is unknown. Caution is advised.

- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, [tachycardia](#), decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, [paralytic ileus](#), confusion, [psychoses](#), agitation, delusions, [delirium](#), and paranoia may be encountered as well as [tachycardia](#), [dysrhythmia](#), and [hypertension](#). In severe cases, immediate medical attention should be obtained.
- 7) Probable Mechanism: additive anticholinergic effect

3.5.1.V] [Bepridil](#)

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

3.5.1.W] [Betel Nut](#)

- 1) Interaction Effect: increased extrapyramidal side effects of [pimozide](#)
- 2) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking [fluphenazine](#) and flupenthixol for [schizophrenia](#)[82]. The extrapyramidal effects were not improved with anticholinergic therapy with [procyclidine](#), and resolved with betel nut discontinuation [82]. A similar effect may occur if betel nut is chewed with concomitant [pimozide](#) therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity [83]. Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation [82].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of [pimozide](#), especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in symptoms of patients with [Parkinson's disease](#) or other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a characteristic red stain on the teeth which may help the clinician discover betel nut use.
- 7) Probable Mechanism: cholinergic effect of betel nut
- 8) Literature Reports

a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized on [fluphenazine](#) decanoate depot 50 milligrams (mg) every 3 weeks for [schizophrenia](#) and [procyclidine](#) 5 mg twice daily for a mild Parkinsonian tremor for the previous 2 years. Within one week of discontinuation of betel

nut chewing, the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of [procyclidine](#) when coadministered with betel nut [78].

b)) A 45-year-old Indian man developed [akathisia](#), tremor and stiffness following betel nut ingestion which was not affected by dosage escalations of up to 20 mg daily of [procyclidine](#). This patient had been previously stabilized on flupenthixol 60 mg depot every two weeks for the previous year for [schizoaffective disorder](#) without extrapyramidal side effects. His symptoms resolved over 4 days after discontinuing betel nut. It appears that the anticholinergic effects of [procyclidine](#) were diminished when betel nut was chewed concomitantly [78].

c)) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent [methscopolamine](#) increased the heart rate and blood pressure of six [Huntington disease](#) patients. Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated a central muscarinic effect for arecoline [79].

d)) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic agent [glycopyrrolate](#) 0.15 mg to 8 patients with [major depressive disorder](#) increased their heart rates. The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p less than 0.05) [80].

e)) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313.7 +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel flower as is commonly done caused significant elevation of [norepinephrine](#) in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and [epinephrine](#) from 62.5 +/- 23.9 pg/mL to 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group [dopamine](#) was also elevated in 8 of 9 subjects, but the mean was not significant [81].

3.5.1.X] Blinatumomab

1)) Interaction Effect: increased CYP450 substrate exposure

2)) Summary: Blinatumomab causes a transient elevation of cytokines which may suppress CYP450 enzyme activities and result in increased exposure of select CYP450 substrates, especially those with a narrow therapeutic index. Risk of interaction is increased during the first 9 days of the first cycle of blinatumomab and the first 2 days of the second cycle. Patients taking blinatumomab together with this drug should be monitored for toxicity or drug concentrations. Dosage of the concomitant drug should be adjusted as needed[187].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Blinatumomab causes a transient elevation of cytokines which may suppress CYP450 enzyme activities and result in increased exposure of select CYP450 substrates, especially those with a narrow therapeutic index. Risk of interaction is increased during the first 9 days of the first cycle of

blinatumomab and the first 2 days of the second cycle. Patients taking blinatumomab together with this drug should be monitored for toxicity or drug concentrations. Dosage of the concomitant drug should be adjusted as needed[187].

7) Probable Mechanism: transient elevation of cytokines by blinatumomab may suppress CYP450 enzyme activities

3.5.1.Y] Boceprevir

1) Interaction Effect: increased pimozone concentrations and risk of cardiac arrhythmias

2) Summary: Boceprevir is a strong inhibitor of CYP3A4/5 isozymes. The coadministration of boceprevir and pimozone is contraindicated as this may result in inhibition of the CYP3A-mediated pimozone metabolism, leading to increased pimozone plasma concentrations and creating the potential for serious and/or life-threatening reactions such as cardiac arrhythmias[183].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of boceprevir and pimozone is contraindicated due to the potential for serious adverse effects including cardiac arrhythmias[183].

7) Probable Mechanism: inhibition of CYP3A-mediated pimozone metabolism

3.5.1.Z] Bromazepam

1) Interaction Effect: increased risk of respiratory or cardiovascular depression

2) Summary: Concomitant use of bromazepam with another CNS depressant should be avoided due to increased risk for respiratory or cardiovascular depression and profound sedation[186].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of bromazepam, which is a CNS depressant, with another CNS depressant may result in respiratory or cardiovascular depression and profound sedation. Due to the added CNS depressant effects, avoid use of bromazepam and other CNS depressants[186].

7) Probable Mechanism: additive CNS depression

3.5.1.AA] Bromocriptine

1) Interaction Effect: decreased bromocriptine efficacy

2) Summary: Concurrent administration of bromocriptine, a potent dopamine receptor agonist, and pimozone, a dopamine antagonist, may cause a potential loss of bromocriptine efficacy[96]. Therefore, the concomitant use of bromocriptine and pimozone should be undertaken with caution.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of bromocriptine, a potent dopamine receptor agonist[96], and pimozone, a dopamine antagonist [3], may result in bromocriptine not working as well [96] and should be undertaken with caution.

7) Probable Mechanism: antagonism at dopamine receptors

3.5.1.AB] Buprenorphine

1) Interaction Effect: increased risk of respiratory depression

- 2) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[126][127] and monitor for signs of [respiratory depression](#), sedation, and hypotension [126].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[126][127] and monitor for signs of [respiratory depression](#), sedation, and hypotension [126].
- 7) Probable Mechanism: additive [respiratory depression](#)

3.5.1.AC| [Bupropion](#)

- 1) Interaction Effect: increased exposure of CYP2D6 substrates
- 2) Summary: Use caution with concurrent administration of [buPROPion](#) (a CYP2D6 inhibitor) and a CYP2D6 substrate as this may increase the exposure of the CYP2D6 substrate[92][93]. Coadministration of [buPROPion](#) and a single dose of [desipramine](#) (a CYP2D6 substrate) resulted in a 2-fold, 5-fold, and 2-fold increase in [desipramine](#) Cmax, AUC, and t1/2, respectively [93]. The CYP2D6 substrate should be initiated at the lower end of the dose range when given with [buPROPion](#). If [buPROPion](#) is added to an existing regimen with a CYP2D6 substrate, consider decreasing the CYP2D6 substrate dose, especially if it has a narrow therapeutic index [92][93]. Monitor for toxicity during coadministration.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of [buPROPion](#) (a CYP2D6 inhibitor) and a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate and should be undertaken with caution. When given with [buPROPion](#) the CYP2D6 substrate should be initiated at the lower end of the dose range. If [buPROPion](#) is added to an existing regimen with a CYP2D6 substrate, consider decreasing the CYP2D6 substrate dose, especially if it has a narrow therapeutic index[92][93]. Monitor for toxicity during coadministration.
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by [buPROPion](#) and its hydroxybupropion metabolite
- 8) Literature Reports

a) Coadministration of [buPROPion](#) 150 mg twice daily and a single dose of [desipramine](#) 50 mg (a CYP2D6 substrate) in healthy volunteers who were extensive 2D6 metabolizers (n=15) resulted in a 2-fold, 5-fold, and 2-fold increase in [desipramine](#) Cmax, AUC, and t1/2, respectively. The effect persisted for 7 days following the last dose of [buPROPion](#) [93].

3.5.1.AD| [Buserelin](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.

7) Probable Mechanism: additive effects on the QT interval

3.5.1.AE] Butorphanol

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [butorphanol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [butorphanol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].

7) Probable Mechanism: additive CNS depression

3.5.1.AF] Ceritinib

1) Interaction Effect: increased exposure of CYP3A substrate

2) Summary: Avoid concomitant use of ceritinib and a CYP3A substrate with a narrow therapeutic index as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate[225].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of ceritinib and a CYP3A substrate with a narrow therapeutic index as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate[225] and monitor patients for toxicity.

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

3.5.1.AG] Chloroquine

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AH| Chlorpromazine

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

3.5.1.AI| Ciprofloxacin

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

3.5.1.AJ| Cisapride

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[107].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [cisapride](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[107].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AK| Citalopram

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

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

3.5.1.AL] [Clarithromycin](#)

- 1) Interaction Effect: an increased risk of QT-interval prolongation
- 2) Summary: Concurrent use of [clarithromycin](#) and [pimozide](#) is contraindicated. [Clarithromycin](#) may inhibit the metabolism of [pimozide](#), resulting in increased [pimozide](#) exposure[238]. Elevated serum levels of [pimozide](#) have been associated with serious or fatal [cardiac arrhythmias](#) (eg, QT-interval prolongation, [ventricular tachycardia](#), [ventricular fibrillation](#), [torsades de pointes](#)) [238][239][240].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [clarithromycin](#) and [pimozide](#) is contraindicated due to the potential for serious or fatal [cardiotoxicity](#), including QT-interval prolongation.
- 7) Probable Mechanism: additive prolongation effects on QT interval
- 8) Literature Reports

a) A case report describes a 27-year-old male with a history of [Tourette syndrome](#) who experienced sudden cardiac death after being co-prescribed [pimozide](#) and [clarithromycin](#). The patient was currently taking [pimozide](#) 14 mg/day, but due to an increase in the number of tics he was experiencing, it was decided that his dose of [pimozide](#) be slowly increased by one 2 mg tablet per day. Two days after the increase in dose, he was diagnosed with [bronchopneumonia](#). [Clarithromycin](#) 500 mg per day was prescribed. Four days after he presented to the emergency department he complained of a racing heart and felt a "head rush". He was observed without incident. An ECG showed a corrected QT interval of 0.506 seconds. He was discharged with instructions to follow-up with his neurologist. The following day he was found unconscious, apneic, and unresponsive without the ability to be resuscitated. Blood [pimozide](#) concentrations were 50 ng/ml (4-20 ng/ml). [Cardiac arrhythmia](#) resulting from an excessive concentration of [pimozide](#) was the most likely cause of death [236].

b) In a randomized, double-blind, placebo-controlled crossover design study, twelve healthy volunteers were given a single oral dose of [pimozide](#) 6 mg after five days of pretreatment with placebo or [clarithromycin](#) 500 mg twice daily. With respect to cytochrome P450 2D6 (CYP2D6) phenotyping, five study subjects were poor metabolizers and seven were extensive metabolizers. All participants had a corrected QTc shorter than 470 ms prior to inclusion in the study. [Clarithromycin](#) pretreatment increased the [pimozide](#) maximum concentration (C_{max}) from 4.4 ng/mL to 6.1 ng/mL and increased the area under the concentration-time curve (AUC) by 113% (146 ng/mL/hr vs. 310 ng/mL/hr). [Pimozide](#) half-life, clearance, and apparent volume of distribution were also significantly increased by [clarithromycin](#). [Pimozide](#) prolonged the QT interval in all study subjects, and these increases coincided with plasma concentrations. In the first 20 hours after administration, the [clarithromycin](#) group had a more prolonged QTc interval (increased by 15.7 ms) than the placebo group (increased by 13.3 ms). There was no significant effect of CYP2D6 phenotyping or gender on the pharmacodynamics or pharmacokinetics of [pimozide](#). [Clarithromycin](#) inhibits cytochrome P450 3A (CYP3A) enzymes, which are responsible for [pimozide](#) metabolism. Inhibition of [pimozide](#) metabolism leads to [cardiotoxicity](#), which is an effect of the parent drug [237].

3.5.1.AM] Clomipramine

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

3.5.1.AN] Clonidine

- 1) Interaction Effect: induction or exacerbation of orthostatic regulation disturbances
- 2) Summary: Coadministration of [clonidine](#) with neuroleptics, such as [pimozide](#)[3], may result in orthostatic regulation disturbance induction or exacerbation [179][180] 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 [pimozide](#)[3], may induce or exacerbate orthostatic regulation disturbances (eg, dizziness, fatigue, orthostatic hypotension) [179][180] and should be approached with caution.
- 7) Probable Mechanism: unknown

3.5.1.AO] Clozapine

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

3.5.1.AP] Cobicistat

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT interval prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Concomitant use of cobicistat , a CYP3A4 inhibitor[133], and [pimozide](#), a CYP3A4 substrate [3], is contraindicated due to the potential for serious or life-threatening [cardiac arrhythmias](#) [133].
- 3) Severity: contraindicated

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of cobicistat and pimozone is contraindicated due to the potential for serious or life-threatening cardiac arrhythmias[133].
- 7) Probable Mechanism: inhibition of CYP3A-mediated pimozone metabolism by cobicistat

3.5.1.AQ] Codeine

- 1) Interaction Effect: increased risk of CNS depression (ie, respiratory depression, profound sedation, coma)
- 2) Summary: The concomitant use of codeine with other CNS depressants may result in profound sedation, respiratory depression, coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for respiratory depression and sedation. Avoid concomitant use of codeine cough medications with CNS depressants[114].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of codeine with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for respiratory depression and sedation. Avoid concomitant use of codeine cough medications with CNS depressants[114].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AR] Conivaptan

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) Summary: Avoid concomitant use of conivaptan (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. Conivaptan increased the AUC of CYP3A substrates midazolam, simvastatin, and amlodipine. The CYP3A substrate may be initiated no sooner than 1 week after completion of conivaptan therapy[200].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of conivaptan (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. The CYP3A substrate may be initiated no sooner than 1 week after completion of conivaptan therapy[200].
- 7) Probable Mechanism: inhibition of CYP3A-mediated substrate metabolism by conivaptan
- 8) Literature Reports

- a) The strong CYP3A inhibitor conivaptan 40 mg/day IV increased the AUC of midazolam, a CYP3A substrate, by approximately 100% with a 1-mg IV dose and by 200% with a 2-mg oral dose [200].
- b) Conivaptan 30 mg/day IV tripled the AUC of simvastatin, a CYP3A substrate [200].
- c) Conivaptan 40 mg orally twice daily doubled the AUC and half-life of amlodipine, a CYP3A substrate [200].

3.5.1.AS] Crizotinib

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

3.5.1.AT] Cyclobenzaprine

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

3.5.1.AU] Dabrafenib

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

3.5.1.AV] Darunavir

- 1) Interaction Effect: an increased risk of serious and/or life-threatening reactions such as [cardiac arrhythmias](#)
- 2) Summary: The coadministration of [darunavir/ritonavir](#) and [pimozide](#) is contraindicated as this may result in inhibition of the CYP3A-mediated [pimozide](#) metabolism, leading to increased [pimozide](#) plasma concentrations and creating the potential for serious and/or life-threatening reactions such as [cardiac arrhythmias](#)[115].

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [darunavir/ritonavir](#) and [pimozide](#) is contraindicated.
- 7) Probable Mechanism: inhibition of CYP3A-mediated [pimozide](#) metabolism

3.5.1.AW] [Dasatinib](#)

- 1) Interaction Effect: increased risk of QT interval prolongation and altered [pimozide](#) plasma concentrations
- 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. Therefore the concurrent administration of [pimozide](#) and a drug that prolongs the QT interval, such as [dasatinib](#)[140], is contraindicated [3]. Additionally, the concomitant use of [dasatinib](#) (a CYP3A4 inhibitor) and [pimozide](#) (a CYP3A4 substrate with a narrow therapeutic index) may result in altered plasma concentrations of [pimozide](#) [141].
- 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 [dasatinib](#)[140], is contraindicated [3]. The concomitant use of [dasatinib](#) and [pimozide](#) may also result in altered [pimozide](#) levels [141].
- 7) Probable Mechanism: additive effects on the QT interval and altered CYP3A4-mediated metabolism of [pimozide](#)

3.5.1.AX] [Degarelix](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.AY] [Delamanid](#)

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

- 6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.AZ] Delavirdine

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#)
- 2) Summary: Delavirdine and [pimozide](#) are both metabolized by the CYP3A4 enzyme system. Competition for this pathway could result in inhibition of [pimozide](#) metabolism, creating the potential for [pimozide](#) toxicity and [cardiac arrhythmias](#). Concurrent administration of delavirdine and [pimozide](#) is contraindicated[146].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of delavirdine and [pimozide](#) is contraindicated due to the potential for serious or life-threatening [cardiac arrhythmias](#).
- 7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.1.BA] Desipramine

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

3.5.1.BB] Deslorelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.BC] Desvenlafaxine

- 1) Interaction Effect: increased exposure of CYP2D6 substrates

2) Summary: Coadministration of desvenlafaxine with a CYP2D6 substrate may result in higher concentrations of the CYP2D6 substrate. When desvenlafaxine 100 mg daily was coadministered with a single 50 mg dose of [desipramine](#), a CYP2D6 substrate, [desipramine](#) C_{max} and AUC did not increase significantly; however, when concurrent desvenlafaxine was increased to 400 mg/day (unapproved dose), the [desipramine](#) C_{max} increased by about 50% and AUC increased by approximately 90%. Therefore, no dose adjustment of the CYP2D6 substrate is needed when coadministering desvenlafaxine 100 mg daily or less; when using a CYP2D6 substrate with desvenlafaxine 400 mg daily (unapproved dosing), reduce the CYP2D6 substrate dose by one-half and increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg is discontinued[104].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of desvenlafaxine (a weak CYP2D6 inhibitor) with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate at desvenlafaxine doses greater than 100 mg/day. Coadministering desvenlafaxine 100 mg/day or less with a CYP2D6 substrate does not require dose adjustment. Reduce the CYP2D6 substrate dose by one-half if used concurrently with desvenlafaxine 400 mg/day (unapproved dosing), and increase the CYP2D6 substrate to the original dose if concurrent desvenlafaxine 400 mg is discontinued[104].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by desvenlafaxine

8) Literature Reports

a) Coadministration of [desipramine](#) (a CYP2D6 substrate) 50 mg with desvenlafaxine 400 mg/day (unapproved dosing) in a clinical study resulted in an increase of approximately 50% for the C_{max} and 90% for the AUC of [desipramine](#). The differences in [desipramine](#) metabolism were not considered clinically relevant when the dose of desvenlafaxine was 100 mg/day (25% increase in C_{max} and 17% in AUC) [104].

3.5.1.BD] [Dihydrocodeine](#)

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [dihydrocodeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[114].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [dihydrocodeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[114].

7) Probable Mechanism: additive CNS depression

3.5.1.BE] [Dirithromycin](#)

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

- 2) Summary: [Dirithromycin](#) may inhibit the metabolism of [pimozide](#), resulting in increased serum concentrations of this agent. Elevated serum levels of [pimozide](#) have been associated with adverse cardiovascular effects including QT interval prolongation, [cardiac arrhythmia](#), and sudden death. The concomitant administration of [pimozide](#) and [dirithromycin](#) is contraindicated[98][99].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent use of [pimozide](#) and [dirithromycin](#) is contraindicated.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.1.BF] [Disopyramide](#)

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

3.5.1.BG] [Dofetilide](#)

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

3.5.1.BH] [Dolasetron](#)

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

3.5.1.BI] Domperidone

- 1) Interaction Effect: increased risk of QT prolongation
- 2) Summary: Coadministration of domperidone and [pimozide](#) is contraindicated[3]. Coadministration may increase the risk of serious cardiac events, including [ventricular arrhythmias](#) and sudden cardiac death. Case-control studies demonstrated an association of serious [ventricular arrhythmias](#) and sudden cardiac death, particularly with domperidone doses greater than 30 mg/day and use of domperidone in patients older than 60 years [214].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant administration of domperidone and [pimozide](#) is contraindicated[3] as this may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years [214].
- 7) Probable Mechanism: additive effects on QT interval prolongation

3.5.1.BJ] Donepezil

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

3.5.1.BK] Doxepin

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

3.5.1.BL] Doxylamine

- 1) Interaction Effect: increased risk of CNS depression

- 2)) Summary: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[229][230]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[229][230]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 7)) Probable Mechanism: additive CNS depression

3.5.1.BM] Dronedaron

- 1)) Interaction Effect: increased risk of [torsade de pointes](#); increased [pimozide](#) plasma levels
- 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 [pimozide](#) is contraindicated. Also, concomitant use of dronedarone (a moderate CYP3A inhibitor) and [pimozide](#) (a CYP3A substrate with narrow therapeutic range) may result in increased [pimozide](#) plasma concentrations[227].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of dronedarone and [pimozide](#) is contraindicated due to the potential of additive effects on the QT interval and an increased risk of [torsade de pointes](#). Also, concomitant use may result in increased [pimozide](#) plasma concentrations[227].
- 7)) Probable Mechanism: additive effects on the QT interval prolongation; inhibition of CYP3A-mediated [pimozide](#) metabolism by dronedarone

3.5.1.BN] Droperidol

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

3.5.1.BO] Ebastine

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

- 6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.BP] [Efavirenz](#)

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

3.5.1.BQ] [Eliglustat](#)

- 1) Interaction Effect: increased CYP2D6 substrate exposure
- 2) Summary: Use caution with coadministration of eliglustat, a CYP2D6 inhibitor, with CYP2D6 substrates, as concurrent use may increase serum concentrations of CYP2D6 substrates. Among patients with [Gaucher disease type 1](#), concurrent use of eliglustat increased mean C_{max} and AUC of [metoprolol](#) (a CYP2D6 substrate) from 1.2- to 1.7-fold in intermediate CYP2D6 metabolizers and 1.6- to 2.3-fold higher than baseline in extensive CYP2D6 metabolizers, respectively. If concurrent use is necessary, monitor therapeutic drug concentrations as clinically indicated, or consider reducing the dose of the CYP2D6 substrate and titrating to clinical effect[169].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of eliglustat with CYP2D6 substrates, as concurrent use may increase serum concentrations of CYP2D6 substrates. If concurrent use is necessary, monitor therapeutic drug concentrations as clinically indicated, or consider reducing the dose of the CYP2D6 substrate and titrating to clinical effect[169].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism by eliglustat
- 8) Literature Reports

a) Among patients with [Gaucher disease type 1](#) who were extensive CYP2D6 metabolizers, mean C_{max} and AUC of [metoprolol](#) (a CYP2D6 substrate) increased by 1.7- and 2.3-fold over baseline, respectively, when used concurrently with eliglustat 127 mg twice daily (unapproved dose) and by 1.2- and 1.6-fold, respectively, in intermediate CYP2D6 metabolizers [169].

3.5.1.BR] [Eluxadoline](#)

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) Summary: Concomitant use of eluxadoline and CYP3A substrates with a narrow therapeutic index may increase exposure of the CYP3A substrate. If coadministered, monitor CYP3A substrate concentrations or other pharmacodynamic markers of drug effect when concomitant use with eluxadoline is initiated or discontinued[118].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of eluxadoline and CYP3A substrates with a narrow therapeutic index may increase exposure of the CYP3A substrate. If coadministered, monitor CYP3A substrate concentrations or other pharmacodynamic markers of drug effect when concomitant use with eluxadoline is initiated or discontinued[118].
- 7) Probable Mechanism: unknown

3.5.1.BS] Enzalutamide

- 1) Interaction Effect: decreased [pimozide](#) exposure
- 2) Summary: Coadministration of enzalutamide, a strong CYP3A4 inducer,[189] and [pimozide](#), a CYP3A4 substrate, [3] may decrease the exposure of [pimozide](#) (a drug with a narrow therapeutic index) and should be avoided [189].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of enzalutamide, a strong CYP3A4 inducer,[189] and [pimozide](#), a CYP3A4 substrate [3] should be avoided as coadministration may decrease the exposure of [pimozide](#), a drug with a narrow therapeutic index [189].
- 7) Probable Mechanism: increased CYP3A4-mediated metabolism of [pimozide](#) by enzalutamide

3.5.1.BT] Eribulin

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

3.5.1.BU] Erythromycin

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

3.5.1.BV] Escitalopram

- 1) Interaction Effect: QTc interval prolongation and an increased risk of [torsade de pointes](#)
- 2) Summary: Coadministration of escitalopram and [pimozide](#) is contraindicated due to a risk of QTc interval prolongation and an increased risk of [torsade de pointes](#). In a controlled study, a single dose of [pimozide](#) 2 mg given with [citalopram](#) 40 mg once daily for 11 days resulted in a mean increase in rate-corrected QT intervals of approximately 10 milliseconds compared with [pimozide](#) given alone[182][3].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of escitalopram and [pimozide](#) is contraindicated due to the potential for QTc interval prolongation and an increased risk of [torsade de pointes](#)[182][3].
- 7) Probable Mechanism: unknown

3.5.1.BW] Famotidine

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

3.5.1.BX] Felbamate

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

3.5.1.BY] Fentanyl

- 1) Interaction Effect: increased risk of CNS depression
- 2) 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[108]. 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](#) [109]. 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 [108].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) 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[108].

7) Probable Mechanism: additive CNS depression

3.5.1.BZ] Fingolimod

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.CA] Flecainide

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.CB] Flibanserin

1) Interaction Effect: additive CNS depression

2) Summary: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[132].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[132].

7) Probable Mechanism: additive CNS depression

3.5.1.CC] Fluconazole

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

2) Summary: The concomitant use of pimozone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of pimozone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.CD] Fluoxetine

1) Interaction Effect: increased pimozone levels and increased risk of QT-interval prolongation and ventricular arrhythmia

2) Summary: The concomitant use of fluoxetine and pimozone may result in elevated pimozone levels and an increased risk of additive QT-interval prolongation via inhibition of CYP2D6-mediated metabolism of pimozone by fluoxetine, a strong CYP2D6 inhibitor[142]. One case of bradycardia and somnolence resulting from concomitant fluoxetine and pimozone therapy has been reported [143]. The concurrent use of fluoxetine and pimozone is contraindicated [142].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Due to the possibility of increased pimozone levels and additive effects of QT-interval prolongation, the concurrent administration of fluoxetine and pimozone is contraindicated[142].

7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of pimozone by fluoxetine; additive effects on QT-interval prolongation

8) Literature Reports

a) One case has been reported in which concurrent use of pimozone 5 mg daily and fluoxetine 20 mg daily in an elderly patient resulted in severe bradycardia and somnolence. The pulse rate gradually returned to normal after discontinuation of pimozone; rechallenge with a lower pimozone dose and a higher fluoxetine dose also resulted in bradycardia [143].

3.5.1.CE] Formoterol

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

2) Summary: The concomitant use of pimozone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

- 6)) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].
- 7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.CF] Fosamprenavir

- 1)) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT interval prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2)) Summary: Fosamprenavir is an inhibitor of the isoenzyme cytochrome P450 3A; concomitant use with [pimozide](#) may result in inhibition of [pimozide](#) metabolism. Elevated [pimozide](#) serum concentrations have been associated with an increased risk of [cardiotoxicity](#). The concurrent administration of [fosamprenavir](#) and [pimozide](#) is contraindicated[190].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: probable
- 6)) Clinical Management: Concomitant use of [fosamprenavir](#) and [pimozide](#) is contraindicated.
- 7)) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.1.CG] Fosaprepitant

- 1)) Interaction Effect: increased plasma concentrations of [pimozide](#)
- 2)) Summary: Fosaprepitant is a prodrug of [aprepitant](#), which is a moderate CYP3A4 inhibitor. Coadministration with [pimozide](#), a CYP3A4 substrate, could result in elevated plasma [pimozide](#) levels and potentially cause serious or life-threatening reactions. The concomitant use of [pimozide](#) and fosaprepitant is contraindicated[181].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of fosaprepitant and [pimozide](#) is contraindicated[181].
- 7)) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [pimozide](#) by [aprepitant](#)

3.5.1.CH] Foscarnet

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

3.5.1.CI] Fosphenytoin

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

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

3.5.1.CJ| [Galantamine](#)

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

3.5.1.CK| [Gatifloxacin](#)

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

3.5.1.CL| [Gemifloxacin](#)

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

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.CM] Golimumab

1J) Interaction Effect: decreased CYP450 substrate exposure

2J) Summary: Golimumab, an antagonist of proinflammatory cytokines, may normalize the formation of CYP450 enzymes that were suppressed during [chronic inflammation](#). Coadministration of golimumab and a CYP450 substrate with a narrow therapeutic index may result in reduced levels of that CYP450 substrate. When initiating or discontinuing golimumab in patients receiving CYP450 substrates with a narrow therapeutic index, monitor drug levels (if available) and therapeutic effect. Dose adjustments of the CYP450 substrate may be needed[172].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Golimumab, an antagonist of proinflammatory cytokines, may normalize the formation of CYP450 enzymes that were suppressed during [chronic inflammation](#). Coadministration of golimumab and a CYP450 substrate with a narrow therapeutic index may result in reduced levels of that CYP450 substrate. When initiating or discontinuing golimumab in patients receiving CYP450 substrates with a narrow therapeutic index, monitor drug levels (if available) and therapeutic effect. Dose adjustments of the CYP450 substrate may be needed[172].

7J) Probable Mechanism: Normalization of CYP450 enzymes formation suppressed during [chronic inflammation](#)

3.5.1.CN] Gonadorelin

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

2J) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.

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

3.5.1.CO] Goserelin

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

2J) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.

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

3.5.1.CP] **Granisetron**

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

2)) Summary: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.CQ] **Halofantrine**

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

2)) Summary: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.CR] **Haloperidol**

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

2)) Summary: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

3)) Severity: contraindicated

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

7)) Probable Mechanism: additive QT-interval prolongation

3.5.1.CS] **Histrelin**

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

2)) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.

- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.CT] Hydrocodone

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: Use caution with the concomitant use of [hydrocodone](#) and a CNS depressant as this may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[117]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [114].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [hydrocodone](#) and a CNS depressant may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[117]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [114].
- 7) Probable Mechanism: additive CNS depression

3.5.1.CU] Hydromorphone

- 1) Interaction Effect: an increase in CNS or [respiratory depression](#)
- 2) Summary: The concomitant use of [HYDROmorphone](#) and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [HYDROmorphone](#) and an antipsychotic together, dose reduction of one or both of the medications should be considered[221].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [HYDROmorphone](#) and other CNS depressants, such as antipsychotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered[221].
- 7) Probable Mechanism: additive CNS depression

3.5.1.CV] Hydroquinidine

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

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

3.5.1.CW] [Hydroxychloroquine](#)

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: [Hydroxychloroquine](#) has been associated with QT interval prolongation[87][88], [ventricular premature contractions](#), and [torsade de pointes](#) [88]. Coadministration of other QT-interval prolonging drugs is contraindicated, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur [89].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: [Hydroxychloroquine](#) has been associated with QT interval prolongation[87][88], [ventricular premature contractions](#), and [torsade de pointes](#) [88]. Coadministration of other QT-interval prolonging drugs is contraindicated, as life-threatening additive effects on the QT interval, including [torsades de pointes](#), may occur [89].
- 7) Probable Mechanism: additive QT interval effects
- 8) Literature Reports

a) Hydroxychloroquine-associated QT interval prolongation was reported in a 41-year-old woman with [congestive heart failure](#) with [systolic left ventricular dysfunction](#). Her comorbidities included [hypertension](#), [systemic lupus erythematosus](#), and [stage 5 chronic kidney disease](#). One week after reinitiation of [hydroxychloroquine](#) therapy, a significant prolongation of the QT interval (QTc 614 msec) was observed during a routine ECG. Following treatment discontinuation of [hydroxychloroquine](#), serial ECGs demonstrated a shortening of the QTc interval. The patient's QTc was 473 msec at a follow up 1 year after discharge [87].

b) QT prolongation and refractory [ventricular arrhythmia](#) were reported with chronic [hydroxychloroquine](#) use in a 67-year-old woman with [systemic lupus erythematosus](#). The patient had been receiving [prednisolone](#), [theophylline](#), and [hydroxychloroquine](#) 200 mg/day for 1 year. The patient had a medical history of [cirrhosis](#), [hepatitis B](#) virus related [hepatoma](#) with portal vein [thrombosis](#), and [asthma](#). The patient experienced a sudden episode of unconsciousness and generalized rigidity while at home. Although the patient regained consciousness within minutes and had no complaints of chest pain, palpitation, limb weakness, incontinence, or confusion, the episode recurred several times. Upon admission the ECG showed multiple [ventricular premature contractions](#), [torsade de pointes](#), and prolongation of the QT interval. Treatment with [hydroxychloroquine](#) was discontinued. Following medical management, [ventricular arrhythmia](#) subsided after 4 days and the QT interval shortened [88].

3.5.1.CX] [Hydroxyzine](#)

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

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

3.5.1.CY| Ibutilide

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

3.5.1.CZ| Idelalisib

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) Summary: Avoid coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects. During a drug interaction study, coadministration of idelalisib and [midazolam](#) (CYP3A substrate) resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax[170].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate should be avoided, as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects[170].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by idelalisib
- 8) Literature Reports

a) During a drug interaction study, administration of idelalisib 150 mg for 15 doses followed by a single dose of [midazolam](#) 5 mg (a CYP3A substrate) in healthy volunteers, resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax [170].

3.5.1.DA| Iloperidone

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

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DB| [Imatinib](#)

1) Interaction Effect: increased plasma levels of [pimozide](#)

2) Summary: Concomitant use of [imatinib](#) and [pimozide](#) should be avoided[167]. Although not studied with [pimozide](#), concomitant administration of [imatinib](#), a CYP3A4 inhibitor, and [simvastatin](#), a CYP3A4 substrate, resulted in 2- and 3.5-fold increases in mean Cmax and AUC values of [simvastatin](#), respectively. A similar interaction can be expected with other CYP3A4 substrates, particularly those with a narrow therapeutic index such as [pimozide](#) [168].

3) Severity: major

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [imatinib](#) and [pimozide](#) should be avoided due to the potential for increased [pimozide](#) plasma concentration, thereby increasing the risk of [pimozide](#) adverse events[167].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [pimozide](#) by [imatinib](#)

3.5.1.DC| [Imipramine](#)

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DD| [Indinavir](#)

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

2) Summary: Indinavir is an inhibitor of cytochrome P450 3A may result in inhibition of [pimozide](#) metabolism. Elevated [pimozide](#) serum concentrations have been associated with an increased risk of [cardiotoxicity](#). The concurrent administration of [indinavir](#) and [pimozide](#) is contraindicated[94].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of [pimozide](#) and [indinavir](#) is contraindicated.

7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.1.DE| [Infliximab](#)

1) Interaction Effect: decreased [pimozide](#) plasma concentrations

2) Summary: In states of [chronic inflammation](#), the formation of CYP450 enzymes is suppressed by increased levels of cytokines such as [tumor necrosis factor \(TNF\) alpha](#). Upon administration of a TNF alpha antagonist, such as [infliximab](#) or [infliximab](#) biosimilar products, the formation of CYP450 enzymes could be normalized. If [infliximab](#) or [infliximab](#) biosimilar products are initiated or discontinued in a patient being treated with a CYP450 substrate with a narrow therapeutic index, such as [pimozide](#), monitor the effects of [pimozide](#) and adjust the dose as needed[212][213].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: If [infliximab](#) or [infliximab](#) biosimilar products are initiated in a patient being treated with a CYP450 substrate with a narrow therapeutic index, such as [pimozide](#), the effectiveness may be reduced due to a possible reduction of [pimozide](#) concentration. Monitor for effectiveness of [pimozide](#) and adjust the dose as needed. Furthermore when [infliximab](#) or [infliximab](#) biosimilar products are discontinued, the concentration of [pimozide](#) may increase and potentially result in toxicity. Monitor for toxicity and consider a dose reduction of [pimozide](#) when [infliximab](#) or [infliximab](#) biosimilar products are discontinued[212][213].

7) Probable Mechanism: increase in CYP450-mediated [pimozide](#) metabolism

3.5.1.DF] Itraconazole

1) Interaction Effect: increased [pimozide](#) exposure and an increased risk of QT prolongation

2) Summary: Coadministration of [itraconazole](#) and [pimozide](#), as well as use for up to 2 weeks of [itraconazole](#) discontinuation is contraindicated as this may increase [pimozide](#) exposure and the risk of serious adverse events[206][207], including prolongation of the QT interval [3].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Coadministration of [itraconazole](#) and [pimozide](#), as well as use for up to 2 weeks of [itraconazole](#) discontinuation is contraindicated as this may increase [pimozide](#) exposure and the risk of serious adverse events[206][207], including prolongation of the QT interval [3].

7) Probable Mechanism: inhibition of CYP3A4-mediated [pimozide](#) metabolism by [itraconazole](#)

3.5.1.DG] Ivabradine

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DH] Kava

1) Interaction Effect: additive [DOPamine](#) antagonist effects

2) Summary: Theoretically, kava may add to the effect of [DOPamine](#) antagonists, increasing the risk for adverse effects. Case reports describe what appears to be DOPamine-blocking activity of kava manifested

in patients as [dystonia](#), [dyskinesias](#), and [Parkinsonism](#)[122][123]. Kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli in mice, suggesting [DOPamine](#) blockade activity [124].

3J) Severity: moderate

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of kava with [DOPamine](#) antagonists. The desired effect and/or adverse effects of the [DOPamine](#) antagonist may be increased or may be variable depending on the time of administration of kava and the quality of the kava product (i.e., whether it contains a standardized amount of kava).

7J) Probable Mechanism: [DOPamine](#) antagonist effect of kava

8J) Literature Reports

aJ) A 27-year-old Aboriginal Australian male presented three times following heavy kava use with symptoms of severe [choreoathetosis](#) of the limbs, trunk, neck, and facial musculature, and athetosis of the tongue. Level of consciousness was not impaired. Symptoms resolved within 12 hours of intravenous [diazepam](#) on each occasion. [Acute rheumatic fever](#) was excluded, cerebrospinal fluid and [computed tomography](#) of the brain was normal, and urinary drug screen was negative. The only abnormalities found in hematological and biochemical tests were a serum [alkaline phosphatase](#) of 162 international units/liter (IU/L) (normal: 35-135 IU/L) and serum gamma-glutamyltransferase of 426 IU/L (normal less than 60 IU/L). These were attributed to kava use. The patient did not drink alcohol [120].

bJ) A 76-year-old female with [idiopathic Parkinson's disease](#) of 17 years' duration treated for 8 years with [levodopa](#) 500 milligrams (mg) and benserazide 125 mg was prescribed kava extract (Kavasporal Forte(R)) 150 mg twice daily for complaints of inner tension. Within 10 days, she noted a pronounced increase in her daily "off" periods both in terms of duration and number. Within 2 days of discontinuing the kava product, symptoms had returned to her normal baseline [121].

cJ) A 63-year-old female experienced sudden and acute forceful involuntary oral and lingual [dyskinesias](#) on the fourth day of self-initiated therapy with kava extract (Kavasporal Forte(R)) 150 mg three times daily. She was treated successfully in the emergency room with [biperiden](#) 5 mg intravenously. She denied taking any other medications in the months preceding this event [121].

dJ) A 22-year-old female took kava extract (Laitan(R)) 100 mg once for anxiety and nervousness. Within four hours she experienced oral and lingual [dyskinesias](#), tonic rotation of the head, and painful twisting trunk movements. She was treated successfully with [biperiden](#) 2.5 mg intravenously. She denied taking any other medications in the months preceding this event [121].

eJ) A 28-year-old male experienced acute involuntary neck extension with forceful upward deviation of the eyes within 90 minutes of taking kava extract (Laitan(R)) 100 mg. Symptoms resolved spontaneously within 40 minutes. This man had a history of acute dystonic reactions following exposure to promethacin (50 mg) and fluspirilene (1.5 mg), which had responded [biperiden](#) 5 mg intravenously 9 and 12 years previously [121].

3.5.1.DI] [Ketoconazole](#)

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

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

3.5.1.DJ] [Lapatinib](#)

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

3.5.1.DK] [Leuprolide](#)

- 1)) Interaction Effect: increased risk of QT-interval prolongation
- 2)) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7)) Probable Mechanism: additive effects on the QT interval

3.5.1.DL] [Levofloxacin](#)

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

3.5.1.DM] Lithium

1) Interaction Effect: weakness, **dyskinesias**, increased extrapyramidal symptoms, **encephalopathy**, and brain damage

2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with **lithium** plus a **DOPamine-2** antagonist, particularly **haloperidol**. A causal relationship between these events and the concomitant administration of a **DOPamine-2** antagonist and **lithium** has not been established[160]. Coadministration of **lithium** and a number of antipsychotic drugs has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and **dyskinesias** in isolated case reports. In most cases, these effects have occurred with therapeutic **lithium** levels [161][162][163]. However, many series and trials have reported using such combinations with no severe adverse consequences [164]. The mechanism is not fully understood, but chronic **lithium** treatment decreases neostriatal DOPaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase [165]. Hyperglycemic reactions have also occurred during combined phenothiazine and **lithium** use [166].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of **DOPamine-2** antagonists, particularly **haloperidol**, and **lithium** are used. Serum **lithium** levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant **haloperidol** and **lithium** therapy has resulted in symptoms of **encephalopathy**, confusion, extrapyramidal symptoms, and fever in several patients with mania [149][150][151]. Irreversible **neurological injuries** have been reported [152][153].

b) Seizures, **encephalopathy**, **delirium**, and abnormal EEG occurred in four patients during combined **lithium** and **thioridazine** therapy [154]. Serum **lithium** levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated **lithium** in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

c) The addition of **lithium** to **neuroleptic therapy** exacerbated extrapyramidal symptoms (EPS) in a small study [155]. The patients had received at least five days of treatment with either oral **thiothixene**, **haloperidol**, or **fluphenazine** in mean doses of 607.5 **chlorpromazine** equivalents prior to initiation of the **lithium** and were experiencing drug-induced extrapyramidal symptoms. Oral **lithium** was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of **lithium**. However, only three patients developed marked symptoms and no patient developed **lithium** toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with **clozapine** and **lithium** were studied [156]. Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, **facial spasms** and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced **delirium**. These effects reversed when **lithium** was discontinued or given at a lower dose. On rechallenge,

one of two patients suffered recurrence of symptoms. By keeping serum [lithium](#) no greater than 0.5 mEq/L, [clozapine](#) could be safely coadministered.

e) [Chlorpromazine](#) serum levels can be significantly reduced in the presence of [lithium](#) treatment. If used concurrently, abrupt cessation of [lithium](#) may result in rebound elevation of [chlorpromazine](#) levels, resulting in [chlorpromazine](#) toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the [lithium](#) may precipitate [chlorpromazine](#) cardiotoxicity. In this report, such toxicity was manifested as sudden [ventricular fibrillation](#) associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation [157].

f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of [DOPamine](#) antagonist antipsychotic drugs and [lithium](#) have been used successfully in many patients with [manic-depressive illness](#). It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms [158].

g) A 69-year-old patient with oxygen-dependent [chronic obstructive pulmonary disorder](#) and a 25-year history of [bipolar disorder](#) was started on [risperidone](#) 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of [lithium](#) (450 mg daily) for more than 10 years. In addition, she was given [amantadine](#) (100 mg twice daily) for tremor. Three weeks after the start of [risperidone](#), the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for [delirium](#). Her [lithium](#) serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her [lithium](#) level decreased to 0.41 mEq/L, she continued to experience profound [delirium](#), tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on [lithium](#) (300 mg at bedtime) because of the onset of mild [hypomania](#). Five days later, she was discharged with a regimen of [lithium](#) and low-dose [lorazepam](#) for treatment of insomnia. It is suggested that [delirium](#) could have been caused by the concurrent use of [lithium](#) and [risperidone](#). Other factors could also have caused [delirium](#), such as the patient's serum [lithium](#) level and the underlying [pulmonary pathology](#). In addition, [amantadine](#), which facilitates the release of presynaptic [DOPamine](#) and has a mild anticholinergic effect, may have contributed [159].

3.5.1.DN] Lithospermum

1) Interaction Effect: decreased effectiveness of [DOPamine](#) antagonists

2) Summary: Theoretically, the [DOPamine](#) agonist activity of lithospermum may oppose that of [DOPamine](#) antagonists, decreasing their effectiveness. Lithospermum likely decreases prolactin secretion via [DOPamine](#) stimulation[203]. Animal data suggest that the effect occurs rapidly within 3 hours after injection, subsiding within 6 to 9 hours [204]. The magnitude and clinical significance of this phenomenon has yet to be determined in humans. Furthermore, it is not known if the ability to stimulate [DOPamine](#) receptors is limited to the hypothalamic region or if such an effect will be noted elsewhere (i.e., if patients with [psychosis](#) will experience worsening of their condition due to [DOPamine](#) stimulation secondary to lithospermum). Caution is recommended until the effects on humans and possible implications of a drug-herb interaction with [DOPamine](#) antagonists can be fully determined.

3) Severity: minor

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: If therapy is initiated with lithospermum and a [DOPamine](#) antagonist, monitor closely for return of symptoms previously controlled by the [DOPamine](#) antagonist.

7J) Probable Mechanism: **DOPamine** agonism of lithospermum may counteract **DOPamine** antagonists

8J) Literature Reports

aJ) Administration of freeze dried extracts (FDE) of *Lithospermum officinale* (Boraginaceae) by **intravenous injection** to rats resulted in reduced prolactin serum levels and hypophyseal stores. When administered diluent, prolactin levels decreased from 36 +/- 8 nanograms/milliliter (ng/mL) serum to 10 +/- 4 ng/mL serum (p less than 0.005) when administered *Lithospermum officinale* FDE (40 milligrams (mg)/100 grams body weight) within 3 hours post intravenous administration. The authors concluded that *Lithospermum officinale* possibly impacted prolactin secretion at the hypothalamic site via **DOPamine** stimulation [201].

bJ) Prolactin levels decreased rapidly below basal values in rats within the first 3 hours following a single **intravenous injection** of *Lithospermum officinale*. Prolactin levels returned to control levels within 6 to 9 hours after the injection [202].

3.5.1.DOJ Lumacaftor

1J) Interaction Effect: reduced exposure to CYP3A substrate

2J) Summary: Lumacaftor is a strong inducer of CYP3A. When lumacaftor was coadministered with ivacaftor, a sensitive CYP3A substrate, ivacaftor exposure was decreased by approximately 80%. Concurrent administration of lumacaftor and a sensitive or narrow therapeutic index CYP3A substrate may decrease the efficacy of the CYP3A substrate and is not recommended[218].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Lumacaftor is a strong inducer of CYP3A. Coadministration of lumacaftor and a sensitive or narrow therapeutic index CYP3A substrate may decrease the efficacy of the CYP3A substrate and is not recommended[218].

7J) Probable Mechanism: induction of CYP3A-mediated metabolism by lumacaftor

3.5.1.DPJ Lumefantrine

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

2J) Summary: Due to the potential for additive effects on QT-interval prolongation, concomitant use of **pimozide** with other drugs that prolong the QT interval, including artemether/lumefantrine, is contraindicated[3]. Coadministration of lumefantrine, a CYP2D6 inhibitor, with **pimozide**, a CYP2D6 substrate, may result in increased **pimozide** plasma levels, further increasing the risk of QT-interval prolongation. Caution is also 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) [234].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of **pimozide** with other drugs that prolong the QT interval, including artemether/lumefantrine, is contraindicated due to the potential for additive effects on QT-interval prolongation[3]. 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) [234].

7J) Probable Mechanism: additive effects on QT-interval prolongation; inhibition of CYP2D6-mediated metabolism of **pimozide**

3.5.1.DQ| Mefloquine

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

3.5.1.DR| Meperidine

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [meperidine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [meperidine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].
- 7) Probable Mechanism: additive CNS depression

3.5.1.DS| Mesoridazine

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[215].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: The concomitant use of [mesoridazine](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[215].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.DT| Methadone

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

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

3.5.1.DU] [Metoclopramide](#)

- 1) Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)
- 2) Summary: Concomitant use of [metoclopramide](#) with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[219]. 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 [220].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [metoclopramide](#) with antipsychotic agents is contraindicated[219]. 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 [220].
- 7) Probable Mechanism: unknown

3.5.1.DV] [Metreleptin](#)

- 1) Interaction Effect: altered exposure to [pimozide](#)
- 2) Summary: Leptin is a cytokine that may alter CYP450 enzyme formation. Use caution with coadministration metreleptin with [pimozide](#) or other CYP450-metabolized drugs with a narrow therapeutic index, as metreleptin-mediated alterations in CYP450 enzyme formation may lead to clinically relevant effects. Monitor [pimozide](#) therapeutic effects or blood concentrations following metreleptin initiation or discontinuation and adjust the [pimozide](#) dose as needed[245].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of metreleptin with [pimozide](#) or other CYP450-metabolized drugs with a narrow therapeutic index, as metreleptin-mediated alterations in CYP450 enzyme formation may lead to clinically relevant effects. Monitor [pimozide](#) therapeutic effects or blood concentrations following metreleptin initiation or discontinuation, and adjust the [pimozide](#) dose as needed[245].
- 7) Probable Mechanism: potential alteration in CYP450 enzyme formation by metreleptin

3.5.1.DW] Metronidazole

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

3.5.1.DX] Miconazole

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: [Miconazole](#) may inhibit the metabolism of [pimozide](#), resulting in increased serum concentrations of this agent. Elevated serum levels of [pimozide](#) have been associated with adverse cardiovascular effects including QT interval prolongation, [cardiac arrhythmia](#), and sudden death. The concurrent use of [miconazole](#) and [pimozide](#) is contraindicated[222].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [miconazole](#) and [pimozide](#) is contraindicated.
- 7) Probable Mechanism: inhibition by [miconazole](#) of cytochrome P450 3A4-mediated [pimozide](#) metabolism

3.5.1.DY] Mifepristone

- 1) Interaction Effect: increased [pimozide](#) plasma concentrations and increased risk for serious [cardiac arrhythmia](#)
- 2) Summary: Both [mifepristone](#) and [pimozide](#) have been associated with QT-interval prolongation[90][3]. The concomitant use of [pimozide](#) (a CYP3A substrate with a narrow therapeutic range) with [mifepristone](#) (a CYP3A inhibitor) is contraindicated due to a risk of increased [pimozide](#) plasma concentrations and adverse events, including serious and/or life-threatening [cardiac arrhythmia](#). Although not specifically studied with [pimozide](#), the coadministration of [simvastatin](#) (another CYP3A substrate) with [mifepristone](#) resulted in an AUC mean ratio (with/without) of 10.4 and 15.7 for [simvastatin](#) and [simvastatin acid](#), respectively, compared with [simvastatin](#) exposure alone. Due to the long terminal half-life of [mifepristone](#) at steady state, at least 2 weeks should pass after stopping [mifepristone](#) (Korlym(TM)) before initiating [pimozide](#) [90].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [mifepristone](#) and [pimozide](#) is contraindicated. Using these agents together may result in increased levels of [pimozide](#), thereby increasing the potential for serious and/or life-threatening [cardiac arrhythmia](#)[90][3]. Wait at least 2 weeks after stopping [mifepristone](#) (Korlym(TM)) before initiating [pimozide](#) [90]

7J) Probable Mechanism: inhibition of CYP3A-mediated [pimozide](#) metabolism by [mifepristone](#); additive effects on QT prolongation

3.5.1.DZJ Milnacipran

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

2J) Summary: Concomitant use of milnacipran and an antipsychotic may result in [hypertension](#), coronary artery vasoconstriction or [serotonin syndrome](#), which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of [serotonin syndrome](#) develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated[231].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of milnacipran and an antipsychotic may result in [hypertension](#) and coronary artery vasoconstriction through additive serotonergic effects. Therefore, use caution when coadministering these agents. If symptoms of [serotonin syndrome](#) develop, discontinue treatment immediately and institute the appropriate supportive symptomatic treatment[231].

7J) Probable Mechanism: additive serotonergic effect

3.5.1.EAJ Mizolastine

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.EBJ Morphine

1J) Interaction Effect: increased risk of [paralytic ileus](#); increased risk of CNS depression

2J) Summary: Coadministration of [morphine](#) and this drug may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). Assess the duration of use and degree of tolerance to CNS depressants prior to concurrent use. If coadministration is clinically necessary, initiate treatment with [morphine](#) at the lowest possible dose (ie, 30 mg every 24 hours or 15 mg every 12 hours) and reduce the dose of 1 or both agents. In addition, monitor patients for sedation, [respiratory depression](#), and signs of urinary retention or reduced gastric motility[111][113][112].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [morphine](#) and this drug may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation

resulting in [paralytic ileus](#). Assess the duration of use and degree of tolerance to CNS depressants prior to concurrent use. If coadministration is clinically necessary, initiate treatment with [morphine](#) at the lowest possible dose (ie, 30 mg every 24 hours or 15 mg every 12 hours) and reduce the dose of 1 or both agents. In addition, monitor patients for sedation, [respiratory depression](#), and signs of urinary retention or reduced gastric motility[111][112][113].

7J) Probable Mechanism: unknown; additive CNS depression

3.5.1.EC| [Morphine Sulfate Liposome](#)

1J) Interaction Effect: increased risk of [paralytic ileus](#); increased risk of CNS depression

2J) Summary: Coadministration of [morphine](#) and this drug may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). Assess the duration of use and degree of tolerance to CNS depressants prior to concurrent use. If coadministration is clinically necessary, initiate treatment with [morphine](#) at the lowest possible dose (ie, 30 mg every 24 hours or 15 mg every 12 hours) and reduce the dose of 1 or both agents. In addition, monitor patients for sedation, [respiratory depression](#), and signs of urinary retention or reduced gastric motility[111][113][112].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of [morphine](#) and this drug may result in additive respiratory and CNS depressant effects. Concomitant use may also cause urinary retention or severe constipation resulting in [paralytic ileus](#). Assess the duration of use and degree of tolerance to CNS depressants prior to concurrent use. If coadministration is clinically necessary, initiate treatment with [morphine](#) at the lowest possible dose (ie, 30 mg every 24 hours or 15 mg every 12 hours) and reduce the dose of 1 or both agents. In addition, monitor patients for sedation, [respiratory depression](#), and signs of urinary retention or reduced gastric motility[111][112][113].

7J) Probable Mechanism: unknown; additive CNS depression

3.5.1.ED| [Moxifloxacin](#)

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.EE| [Nafarelin](#)

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

2J) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.

3J) Severity: contraindicated

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.EF] Nefazodone

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsades de pointes**, **cardiac arrest**)
- 2) Summary: **Nefazodone** may inhibit the metabolism of **pimozide**, resulting in increased serum concentrations of this agent. Elevated serum levels of **pimozide** have been associated with adverse cardiovascular effects including QT interval prolongation, **cardiac arrhythmia**, and sudden death. The concurrent use of **nefazodone** and **pimozide** is contraindicated[224].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: The concurrent administration of **nefazodone** and **pimozide** is contraindicated.
- 7) Probable Mechanism: inhibition by **nefazodone** of cytochrome P450 3A-mediated **pimozide** metabolism

3.5.1.EG] Nelfinavir

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT interval prolongation, **torsades de pointes**, **cardiac arrest**)
- 2) Summary: Nelfinavir is an inhibitor of cytochrome P450 3A may result in inhibition of **pimozide** metabolism. Elevated **pimozide** serum concentrations have been associated with an increased risk of **cardiotoxicity**. The concurrent administration of **nelfinavir** and **pimozide** is contraindicated[208].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of **pimozide** and **nelfinavir** is contraindicated.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated **pimozide** metabolism

3.5.1.EH] Nilotinib

- 1) Interaction Effect: increased exposure of CYP3A4 substrate and increased risk of QT-interval prolongation
- 2) Summary: Nilotinib is a moderate CYP3A4 inhibitor and is independently capable of prolonging the QT interval. Avoid use of nilotinib with CYP3A4 substrates that also prolong the QT interval as concomitant use may lead to increased exposure to the CYP3A4 substrate and an increased risk of QT-interval prolongation and **torsade de pointes**. If possible, treatment with nilotinib should be interrupted. If concurrent treatment is required, close monitoring for QT interval prolongation is recommended and dose adjustments of the CYP3A4 substrate may be necessary[247]. Monitoring for toxic effects should be considered.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Nilotinib is a moderate CYP3A4 inhibitor and is independently capable of prolonging the QT interval. Use of nilotinib with CYP3A4 substrates that also prolong the QT interval

should be avoided, as concomitant use may lead to increased exposure to the CYP3A4 substrate and an increased risk of QT-interval prolongation and *torsade de pointes*. If possible, treatment with nilotinib should be interrupted. If concurrent treatment is required, close monitoring for QT interval prolongation is recommended and dose adjustments of the CYP3A4 substrate may be necessary[247]. Monitoring for toxic effects should be considered.

7J) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by nilotinib; additive QT-interval prolongation

3.5.1.EI] **Norfloxacin**

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

2J) Summary: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.EJ] **Octreotide**

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

2J) Summary: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.EK] **Ofloxacin**

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

2J) Summary: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of **pimozide** with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious **ventricular arrhythmias**[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.EL] Olanzapine

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

3.5.1.EM] Ondansetron

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

3.5.1.EN] 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, monitor the patient and decrease the dose of 1 or both drugs[128]. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage [129][130].
- 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, monitor the patient and decrease the dose of 1 or both drugs[128]. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage [129][130].
- 7) Probable Mechanism: additive CNS depression effects

3.5.1.EO] Oxymorphone

- 1) Interaction Effect: increased risk of [respiratory depression](#), profound sedation, coma, and death
- 2) 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[228].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) 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[228].
- 7) Probable Mechanism: additive respiratory and CNS depressant effects

3.5.1.EP] [Paliperidone](#)

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

3.5.1.EQ] [Panobinostat](#)

- 1) Interaction Effect: increased [pimozide](#) exposure; increased risk of QT interval prolongation
- 2) Summary: Concomitant use of panobinostat (a CYP2D6 inhibitor)[246] and [pimozide](#) (a CYP2D6 substrate) is contraindicated. Using these agents together may result in increased levels of [pimozide](#), thereby increasing the potential for serious and/or life-threatening QT interval prolongation [1].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of panobinostat (a CYP2D6 inhibitor)[246] and [pimozide](#) (a CYP2D6 substrate) is contraindicated. Using these agents together may result in increased levels of [pimozide](#), thereby increasing the potential for serious and/or life-threatening QT interval prolongation [1].
- 7) Probable Mechanism: inhibition of CYP2D6-mediated [pimozide](#) metabolism by panobinostat; additive effects on QT interval

3.5.1.ER] [Paroxetine](#)

- 1) Interaction Effect: an increased risk of [pimozide](#) toxicity including [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Coadministration of [paroxetine](#) and [pimozide](#) is contraindicated. A controlled study involving concurrent administration of [pimozide](#) and [paroxetine](#) to healthy volunteers resulted in a mean increase in AUC and Cmax of 151% and 62%, respectively. The consequence of such an extreme increase

of pimozone plasma concentrations may be pimozone toxicity, including risk of QT prolongation leading to *torsades de pointes*[216][217].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The concurrent administration of paroxetine and pimozone is contraindicated due to the possibility of significantly increased pimozone plasma concentrations resulting in a dangerous risk of pimozone toxicity[216][217].

7) Probable Mechanism: inhibition of CYP2D6-mediated pimozone metabolism by paroxetine

8) Literature Reports

a) A group of healthy volunteers in a controlled study received a single dose of 2 mg pimozone after being titrated up to a daily dose of 60 mg of immediate-release paroxetine hydrochloride. The study resulted in a mean increase of pimozone AUC and Cmax of 151% and 62%, respectively, compared to pimozone administered alone [216][217].

3.5.1.ES] Pasireotide

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

2) Summary: The concomitant use of pimozone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of pimozone with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious ventricular arrhythmias[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.ET] Pazopanib

1) Interaction Effect: increased pimozone concentrations and risk of QT prolongation

2) Summary: The concomitant use of pazopanib, a weak CYP3A4 inhibitor, and pimozone, a CYP3A4 substrate, may increase the concentrations of pimozone resulting in increased pimozone-related adverse events, including potential for QT prolongation and an increased risk for serious cardiac side effects[145] [185]. The coadministration of these agents is contraindicated [145].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: There have been reports of prolonged QT interval and *torsades de pointes* with pazopanib[185]. The concomitant use of other drugs that prolong the QT interval, such as pazopanib, and pimozone is contraindicated [145]. Using these agents together may increase the concentrations of pimozone resulting in the risk for pimozone-related adverse events including the potential for QT interval prolongation and an increased risk for serious cardiac side effects [185][145].

7) Probable Mechanism: inhibition of CYP3A4-mediated pimozone metabolism and additive effect on QT interval

3.5.1.EU] Pentamidine

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

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

3.5.1.EV] [Pentazocine](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [pentazocine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [pentazocine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].
- 7) Probable Mechanism: additive CNS depression

3.5.1.EW] [Perflutren Lipid Microsphere](#)

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

3.5.1.EX] [Periciazine](#)

- 1) Interaction Effect: risk of enhanced CNS depression
- 2) Summary: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[175][176].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[175][176].
- 7) Probable Mechanism: additive CNS depression

3.5.1.EY] Perphenazine

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

3.5.1.EZ] Phenylalanine

- 1) Interaction Effect: increased incidence of tardive dyskinesia
- 2) Summary: Taking phenylalanine concomitantly with certain neuroleptic drugs may exacerbate tardive dyskinesia[106]. Abnormal phenylalanine metabolism in certain patients may lead to phenylalanine accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines [106].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised if phenylalanine is administered with a neuroleptic agent. Monitor the patient closely for signs of tardive dyskinesia.
- 7) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis
- 8) Literature Reports

a) Phenylalanine tended to increase the incidence of tardive dyskinesia in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with unipolar depression with tardive dyskinesia (n=11), (2) patients with no tardive dyskinesia with current or past exposure to greater than or equal to 100 milligrams (mg) of a chlorpromazine equivalent for at least 3 months (n=10), and (3) patients with no tardive dyskinesia not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered phenylalanine 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to phenylalanine administration and 2 hours after administration. Three patients in group 1 (with tardive dyskinesia) had the highest postloading phenylalanine plasma levels, this group as a whole had higher (though nonsignificant) mean phenylalanine levels than the other groups. Tardive dyskinesia score (measured using the Abnormal Involuntary Movements Scale (AIMS)) nonsignificantly increased in group 1. Postloading phenylalanine level and postloading AIMS

scores were significantly positively correlated in group 1 ($r_s=0.347$, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading [phenylalanine](#) level and baseline AIMS scores demonstrated a trend toward correlation ($r_s=0.246$, $p=0.092$; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, [phenylalanine](#) loading increased plasma [phenylalanine](#) levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of [phenylalanine](#) to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly [105].

3.5.1.FA] Pimavanserin

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

3.5.1.FB] Pipamperone

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

3.5.1.FC] Piperaquine

- 1) Interaction Effect: increased exposure of CYP3A4 substrates and increased risk of QT-interval prolongation
- 2) Summary: Concomitant administration of piperaquine and QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperaquine administration, is contraindicated. Concurrent administration of piperaquine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperaquine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperaquine therapy[116].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of piperazine (a QT-interval prolonging drug) with other QT-interval prolonging drugs may result in additive prolongation effects on the QT interval and is contraindicated. Additionally, recent use of QT-interval prolonging drugs, that may still be circulating at the time of piperazine administration, is contraindicated. Concurrent administration of piperazine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperazine, caution is advised when administering a CYP3A4 substrate for up to 3 months after discontinuation of piperazine therapy[116].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of this drug by piperazine; additive QT-interval prolongation

3.5.1.FD] Pitolisant

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.FE] Pixantrone

1) Interaction Effect: increased exposure of CYP1A2 substrates

2) Summary: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[173].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[173].

7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by pixantrone

3.5.1.FF] [Posaconazole](#)

1) Interaction Effect: increased [pimozide](#) plasma concentrations and increased risk of QT interval prolongation

2) Summary: The metabolism of [pimozide](#), a CYP3A4 substrate, may be inhibited by concomitant administration of [posaconazole](#), a strong CYP3A4 inhibitor. Increased [pimozide](#) plasma concentrations can lead to QT interval prolongation and [torsade de pointes](#). Prolongation of the QT interval and rare cases of [torsade de pointes](#) have also been reported in patients receiving [posaconazole](#). Therefore, concomitant use of [posaconazole](#) and CYP3A4 substrates that prolong the QT interval is contraindicated[97].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

- 6)) Clinical Management: Concomitant use of [posaconazole](#) with CYP3A4 substrates that prolong the QT interval, such as [pimozide](#), is contraindicated due to the potential for increased [pimozide](#) plasma concentrations, thereby increasing the risk for QT interval prolongation and [torsades de pointes](#)[97].
- 7)) Probable Mechanism: inhibition of CYP3A4-mediated [pimozide](#) metabolism by [posaconazole](#)

3.5.1.FG] [Probucol](#)

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

3.5.1.FH] [Procainamide](#)

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

3.5.1.FI] [Prochlorperazine](#)

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

3.5.1.FJ] [Promethazine](#)

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

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

3.5.1.FK] [Propafenone](#)

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

3.5.1.FL] [Protriptyline](#)

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

3.5.1.FM] [Quetiapine](#)

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

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.FN] Quinidine

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.FO] Quinine

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

2J) Summary: Both [pimozide](#) and [quinine](#) have been associated with QT interval prolongation and [torsades de pointes](#)[145][144]. [Quinine](#) is primarily metabolized by CYP3A4 and may also inhibit the metabolism of CYP3A4 substrates, such as [pimozide](#) [144]. Due to the potential for additive effects on the QT interval, the concomitant use of [pimozide](#) and other drugs that prolong the QT interval, such as [quinine](#), is contraindicated [145].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) and [quinine](#) is contraindicated due to potential inhibition of [pimozide](#) metabolism and a risk of additive QT interval prolongation[144].

7J) Probable Mechanism: inhibition of CYP3A4-mediated [pimozide](#) metabolism and additive effect on QT interval

3.5.1.FP] Ranolazine

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.FQ] Remifentanyl

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

2) Summary: The concomitant use of [remifentanyl](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [remifentanyl](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].

7) Probable Mechanism: additive CNS depression

3.5.1.FR] Rilonacept

1) Interaction Effect: altered [pimozide](#) plasma concentrations

2) Summary: In states of [chronic inflammation](#), the formation of CYP450 enzymes is suppressed by increased levels of cytokines such as interleukin-1 (IL-1). Upon administration of an IL-1 blocker, such as rilonacept, the formation of CYP450 enzymes could be normalized. In patients receiving CYP450 substrates with a narrow therapeutic index concomitantly, such normalization may have a clinically relevant effect on the CYP450 substrate levels. If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate that has a narrow therapeutic index, such as [pimozide](#), the therapeutic effect of [pimozide](#) should be monitored and [pimozide](#) dose should be adjusted if necessary[188].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: If rilonacept therapy is initiated in a patient being treated with a CYP450 substrate with a narrow therapeutic index, such as [pimozide](#), monitor for therapeutic effect of [pimozide](#) and adjust [pimozide](#) dose as needed[188].

7) Probable Mechanism: interference with CYP450-mediated [pimozide](#) metabolism

3.5.1.FS] Risperidone

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.FT] Ritonavir

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

2) Summary: [Ritonavir](#) is an inhibitor of CYP3A4 and inhibition of [pimozide](#) metabolism may result from coadministration. Elevated [pimozide](#) serum concentrations have been associated with an increased risk of [cardiotoxicity](#). Concomitant use of [ritonavir](#) and [pimozide](#) is contraindicated[1] due to the potential for serious or life-threatening reactions, including [cardiac arrhythmias](#) [101][102][103].

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Concomitant use of [pimozide](#) and [ritonavir](#) is contraindicated due to the potential for serious or life-threatening reactions, including [cardiac arrhythmias](#)[101][102][103].

7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.1.FU] Rolapitant

1) Interaction Effect: Increased plasma concentration of [pimozide](#)

2) Summary: Concomitant use of rolapitant (a moderate CYP2D6 inhibitor) and [pimozide](#) (a CYP2D6 substrate) should be avoided as increased levels of [pimozide](#) may result in QT prolongation. Inhibition of the CYP2D6 enzyme has been observed 7 days after a single dose of rolapitant and may last longer. If coadministration cannot be avoided, monitor for adverse events[232].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of rolapitant (a moderate CYP2D6 inhibitor) and [pimozide](#) (a CYP2D6 substrate) should be avoided as increased levels of [pimozide](#) may result in QT prolongation. Inhibition of the CYP2D6 enzyme has been observed 7 days after a single dose of rolapitant and may last longer. If coadministration cannot be avoided, monitor for adverse events[232].

7) Probable Mechanism: Inhibition of CYP2D6-mediated [pimozide](#) metabolism by rolapitant

3.5.1.FV] Saquinavir

1) Interaction Effect: increased [pimozide](#) plasma concentrations and increased risk for serious [cardiac arrhythmia](#)

2) Summary: [Pimozide](#) and [saquinavir](#) are both metabolized primarily by CYP3A4 and are associated with QT interval prolongation. Additionally, ritonavir-boosted [saquinavir](#) is a potent CYP3A inhibitor. Using these agents together may increase the exposure of [pimozide](#), with the potential for serious and/or life-threatening [cardiac arrhythmia](#). Therefore, the concomitant use of [pimozide](#) and ritonavir-boosted [saquinavir](#) is contraindicated[233][145].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [pimozide](#) and ritonavir-boosted [saquinavir](#) is contraindicated. Using these agents together may result in increased levels of [pimozide](#), thereby increasing the potential for serious and/or life-threatening [cardiac arrhythmia](#)[233][145].

7) Probable Mechanism: inhibition of CYP3A-mediated [pimozide](#) metabolism by [saquinavir](#); additive effects on QT prolongation

3.5.1.FW] Secukinumab

1) Interaction Effect: decreased CYP450 substrate exposure

2) Summary: Secukinumab, an antagonist of the cytokine interleukin (IL)-17A, may normalize the formation of CYP450 enzymes that were suppressed during [chronic inflammation](#). Coadministration of secukinumab and a CYP450 substrate may result in reduced CYP450 substrate levels. When initiating

or discontinuing secukinumab in patients receiving CYP450 substrates with a narrow therapeutic index, consider monitoring drug levels (if available) and therapeutic effect. Dose adjustments of CYP450 substrates may be needed[95].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Secukinumab, an antagonist of the cytokine interleukin (IL)-17A, may normalize the formation of CYP450 enzymes that were suppressed during [chronic inflammation](#). Coadministration of secukinumab and a CYP450 substrate may result in reduced CYP450 substrate levels. When initiating or discontinuing secukinumab in patients receiving CYP450 substrates with a narrow therapeutic index, consider monitoring drug levels (if available) and therapeutic effect. Dose adjustments of CYP450 substrates may be needed[95].

7J) Probable Mechanism: normalization of CYP450 enzymes formation suppressed during [chronic inflammation](#)

3.5.1.FX] [Selegiline](#)

1J) Interaction Effect: loss of [selegiline](#) efficacy

2J) Summary: Use caution with coadministration of [selegiline](#), an MAOI, with this drug, a [dopamine](#) antagonist, as concurrent use may reduce [selegiline](#) efficacy[226].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with coadministration of [selegiline](#) with this drug, a [dopamine](#) antagonist, as concurrent use may reduce [selegiline](#) efficacy[226].

7J) Probable Mechanism: dopaminergic antagonist effects

3.5.1.FY] [Sertindole](#)

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.FZ] [Sertraline](#)

1J) Interaction Effect: an increase in plasma [pimozide](#) levels

2J) Summary: Due to the narrow therapeutic index of [pimozide](#) and due to the interaction noted at low dose of [pimozide](#), concomitant administration of [sertraline](#) and [pimozide](#) is contraindicated[244].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Concomitant use of [sertraline](#) in patients taking [pimozide](#) is contraindicated.

7J) Probable Mechanism: unknown

8) Literature Reports

a) In a controlled trial of a single 2 mg dose of [pimozide](#), [sertraline](#) 200 mg daily coadministration to steady state was associated with a mean increase in [pimozide](#) area under the concentration-time curve (AUC) and maximum plasma concentrations (C_{max}) of about 40%, but was not associated with any changes in EKG. Since the highest recommended [pimozide](#) dose (10 mg) has not been evaluated in combination with [sertraline](#), the effect on QT interval and pharmacokinetic parameters at higher than 2 mg are not known. Considering the narrow therapeutic index of [pimozide](#) and observed interaction data with low doses, the combination should be avoided [243].

3.5.1.GA] [Sevoflurane](#)

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

3.5.1.GB] [Siltuximab](#)

- 1) Interaction Effect: decreased effectiveness of CYP450 substrate
- 2) Summary: Coadministration of siltuximab and a CYP450 substrate with a narrow therapeutic index may increase the metabolism of the substrate and decrease its effectiveness. Approach concurrent use with caution. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation. If coadministration is required, perform therapeutic monitoring and adjust dose of substrate as needed[110].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of siltuximab and a CYP450 substrate with a narrow therapeutic index may increase the metabolism of the substrate and decrease its effectiveness. Use caution when coadministering siltuximab and this drug. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation. If coadministration is required, perform therapeutic monitoring and adjust dose of substrate as needed[110].
- 7) Probable Mechanism: inhibition of interleukin-6 by siltuximab increases CYP450 levels leading to increased metabolism of CYP450 substrates

3.5.1.GC] [Sodium Phosphate](#)

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

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

3.5.1.GD] [Sodium Phosphate, Dibasic](#)

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

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

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

3.5.1.GF] [Solifenacin](#)

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

3.5.1.GG] [Sorafenib](#)

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

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

3.5.1.GH] [Sotalol](#)

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

3.5.1.GI] [Sparfloxacin](#)

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

3.5.1.GJ] [Sufentanil](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [sufentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [sufentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[114].

7) Probable Mechanism: additive CNS depression

3.5.1.GK] Sulpiride

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.GL] Sultopride

1) Interaction Effect: [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))

2) Summary: Coadministration of drugs that potentially prolong the QTc interval, such as [pimozide](#) and sultopride, should be approached with caution[196][197][198][199].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of [pimozide](#) and other agents that prolong the QT interval, such as sultopride, is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

8) Literature Reports

a) In experimental studies of conditions other than [Tourette's Disorder](#), sudden, unexpected deaths have occurred. The patients were receiving [pimozide](#) dosages of approximately 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to [ventricular arrhythmia](#). The manufacturer recommends that an [electrocardiogram](#) be performed before [pimozide](#) treatment is initiated and periodically thereafter, especially during the period of dose adjustment [192].

b) Sultopride may induce prolongation of the QT interval and [ventricular arrhythmias](#) including [torsades de pointes](#) following therapeutic or toxic doses [193][194][195].

3.5.1.GM] Sunitinib

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

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

3.5.1.GN] [Tacrolimus](#)

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

3.5.1.GO] [Tamoxifen](#)

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

3.5.1.GP] [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 of [respiratory depression](#), hypotension, and sedation[223].
- 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[223].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.GQ| Telaprevir

1J) Interaction Effect: increased [pimozide](#) concentrations

2J) Summary: Telaprevir is an inhibitor of CYP3A isozymes. The coadministration of [pimozide](#) and telaprevir is contraindicated as this may result in inhibition of the CYP3A-mediated [pimozide](#) metabolism, leading to increased [pimozide](#) plasma concentrations and creating the potential for serious and/or life-threatening reactions such as [cardiac arrhythmias](#)[148].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [pimozide](#) and telaprevir is contraindicated due to the potential for serious adverse effects including [cardiac arrhythmias](#)[148].

7J) Probable Mechanism: inhibition of CYP3A-mediated [pimozide](#) metabolism

3.5.1.GR| Telavancin

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.GS| Telithromycin

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.GT| Terfenadine

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

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

3.5.1.GU] Tetrabenazine

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

3.5.1.GV] Thioridazine

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

3.5.1.GW] Tiotropium

- 1)) Interaction Effect: increased risk of anticholinergic side effects
- 2)) Summary: Treatment with both [tiotropium](#) and this drug may produce additive anticholinergic effects. Avoid concomitant use with other anticholinergic agents[191].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Treatment with both [tiotropium](#) and this drug may produce additive anticholinergic effects. Avoid concomitant use with other anticholinergic agents[191].
- 7)) Probable Mechanism: additive anticholinergic effects

3.5.1.GX] Tipranavir

- 1) Interaction Effect: serious and/or life-threatening reactions such as [cardiac arrhythmias](#)
- 2) Summary: Because of the potential for serious and/or life-threatening [cardiac arrhythmias](#) that can occur with increased plasma concentrations of [pimozide](#), the concurrent use of [tipranavir](#) and [ritonavir](#) with [pimozide](#) is contraindicated. [Tipranavir](#), coadministered with 200 milligrams of [ritonavir](#), is a net inhibitor of cytochrome P450 3A. Concomitant administration of [tipranavir](#) and [ritonavir](#) with [pimozide](#), which is metabolized by cytochrome P450 3A4 enzymes, could result in an increased plasma concentration of [pimozide](#) and is contraindicated[91].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [tipranavir](#) and [ritonavir](#), when coadministered with [pimozide](#) is contraindicated.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.1.GY] Tizanidine

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

3.5.1.GZ] Tocilizumab

- 1) Interaction Effect: altered [pimozide](#) plasma concentrations
- 2) Summary: In states of [chronic inflammation](#), the formation of CYP450 enzymes is suppressed by increased levels of cytokines such as interleukin-6 (IL-6). Upon administration of an IL-6 receptor inhibitor, such as tocilizumab, the formation of CYP450 enzymes could be normalized. In patients receiving CYP450 substrates with a narrow therapeutic index (such as [pimozide](#)) concomitantly with tocilizumab, such normalization may have a clinically relevant effect on [pimozide](#) levels through an increase in CYP450-mediated [pimozide](#) metabolism. If tocilizumab therapy is initiated in a patient being treated with a CYP450 substrate that has a narrow therapeutic index, such as [pimozide](#), the therapeutic effect of [pimozide](#) should be monitored, and the [pimozide](#) dose should be adjusted if necessary[235].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: If tocilizumab therapy is initiated in a patient being treated with a CYP450 substrate with a narrow therapeutic index, such as [pimozide](#), monitor for therapeutic effect of [pimozide](#) and adjust [pimozide](#) dose as needed[235].
- 7) Probable Mechanism: increase in CYP450-mediated [pimozide](#) metabolism

3.5.1.HA| Tolterodine

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

3.5.1.HB| Toremifene

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

3.5.1.HC| Tramadol

- 1) Interaction Effect: an increased risk of seizures
- 2) Summary: Seizures have been reported in patients using [tramadol](#). The manufacturer of [tramadol](#) states that combining neuroleptic medications with [tramadol](#) may enhance the risk of seizures[125].
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution should be used if [tramadol](#) is to be administered to patients receiving [neuroleptic therapy](#). If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
- 7) Probable Mechanism: unknown

3.5.1.HD| Trazodone

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

- 6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].
- 7) Probable Mechanism: additive QT-interval prolongation

3.5.1.HE] Trimipramine

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

3.5.1.HF] Triptorelin

- 1) Interaction Effect: increased risk of QT-interval prolongation
- 2) Summary: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86]. Coadministration of gonadotropin-releasing (GnRH) agonists with certain QT-interval prolonging drugs is contraindicated because of the risk for additive effects on the QT interval.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Androgen deprivation caused by gonadotropin-releasing hormone (GnRH) agonists may prolong the QT interval[84][85][86], and coadministration of GnRH agonists with certain QT-interval prolonging drugs is contraindicated.
- 7) Probable Mechanism: additive effects on the QT interval

3.5.1.HG] Troleandomycin

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Troleandomycin may inhibit the metabolism of [pimozide](#), resulting in increased serum concentrations of this agent. Elevated serum concentrations of [pimozide](#) have been associated with adverse cardiovascular effects, including QT interval prolongation, [cardiac arrhythmias](#), and sudden death. The concomitant administration of [pimozide](#) and troleandomycin is contraindicated[177][178].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Concurrent use of [pimozide](#) and troleandomycin is contraindicated.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.1.HH] Vandetanib

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

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

3.5.1.HI| [Vardenafil](#)

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

3.5.1.HJ| [Vemurafenib](#)

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

3.5.1.HK| [Venlafaxine](#)

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

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.HLJ Vilanterol

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.HMJ Vinflunine

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

2J) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7J) Probable Mechanism: additive QT-interval prolongation

3.5.1.HNJ Vitex

1J) Interaction Effect: decreased effectiveness of [DOPamine](#) antagonists

2J) Summary: Theoretically, the [DOPamine](#) agonist activity of Vitex may oppose that of [DOPamine](#) antagonists, decreasing their effectiveness. Vitex has been effective in alleviating [luteal phase defects](#) due to [hyperprolactinemia](#) and in relieving symptoms related to [premenstrual tension syndrome](#)[137][138]. Vitex reduced prolactin secretion in humans [137]. In vitro, Vitex inhibited prolactin release by binding to the D2 receptor [139].

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: established

6J) Clinical Management: If therapy is initiated with Vitex and a [DOPamine](#) antagonist, monitor closely for return of symptoms previously controlled by the [DOPamine](#) antagonist.

7J) Probable Mechanism: [DOPamine](#) agonism of Vitex may counteract [DOPamine](#) antagonists

8J) Literature Reports

aJ) Vitex agnus castus (Vitex) effectively normalized prolactin release in a randomized double-blind, placebo-controlled trial of 52 women with [luteal phase defects](#) due to latent [hyperprolactinemia](#). Administration of Vitex agnus castus 20 mg daily for three months reduced prolactin release (from 23.7 to 22.5 nanogram (ng)/mL; p equal to 0.23), normalized shortened luteal phases (from 5.5 days to 10.5 days; p less than 0.005), and eliminated deficits in luteal

progesterone synthesis (from 2.46 ng/mL to 9.69 ng/mL; p less than 0.001). No side effects were noted [134].

b) Vitex agnus castus and **pyridoxine** caused a similar reduction on the **premenstrual tension** scale (PMTS) in a randomized, controlled trial of 127 women with PMTS. Patients taking Vitex agnus castus (Agnolyt(R)) experienced more relief from breast tenderness, inner tension, headache, edema, constipation, and depression than those taking **pyridoxine**. Patients in the Vitex agnus castus group receive one capsule of Agnolyt(R) and one placebo capsule daily for 3 menstrual cycles. Patients in the **pyridoxine** group received one placebo capsule twice daily on days 1-15 of the menstrual cycle and **pyridoxine** 100 mg twice daily on days 16 to 35 of the menstrual cycle for 3 menstrual cycles. Unspecified gastrointestinal disturbances occurred in the treatment group along with two cases of skin reaction and one transient headache [135].

c) In vitro, Vitex (Agnus castus) was found to bind to the D2 receptor in rat pituitary cell cultures. Basal prolactin release was significantly inhibited by 0.5 milligram (mg) and 1 mg of vitex extract/mL culture medium (p less than 0.05). Agnus castus extract doses from 0.125 mg/mL to 1 mg/mL significantly suppressed prolactin release in cells stimulated by thyrothropin releasing hormone (TRH) (p less than 0.05). DOPaminergic action was demonstrated in the rat corpus striatum membrane **DOPamine** receptor assay. Agnus castus extract did not affect basal **luteinizing hormone** (LH) or **follicle-stimulating hormone** (FSH), indicating selectivity for prolactin secretion, and not generalized inhibition of pituitary hormone secretion. The effect was not due to a cytotoxic effect as demonstrated by the lack of effect on the MTT-conversion test. The authors concluded that Agnus castus exerted its prolactin inhibiting effect via stimulation of D2 receptors in the pituitary [136].

3.5.1.HO] **Voriconazole**

- 1) Interaction Effect: an increased risk of **cardiotoxicity** (QT prolongation, **torsade de pointes**, **cardiac arrest**)
- 2) Summary: The systemic exposure to **pimozide** may be significantly increased by concomitant administration of **voriconazole**. The metabolism of **pimozide** may be inhibited by concomitant administration of **voriconazole**. Increased plasma concentrations of **pimozide** can lead to QT prolongation and rare occurrence of **torsade de pointes**[184].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of **voriconazole** and **pimozide** is contraindicated[184].
- 7) Probable Mechanism: inhibition by **voriconazole** of cytochrome P450 3A4-mediated **pimozide** metabolism

3.5.1.HP] **Vorinostat**

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

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.HQ| Zileuton

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

2) Summary: [Zileuton](#) may inhibit the metabolism of [pimozide](#), resulting in increased serum concentrations of this agent. Elevated serum levels of [pimozide](#) have been associated with adverse cardiovascular effects including QT interval prolongation, [cardiac arrhythmia](#), and sudden death. The concurrent use of [zileuton](#) or any inhibitor of cytochrome P450 3A enzymes and [pimozide](#) is not recommended[205].

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: The concurrent administration of [pimozide](#) with an inhibitor of cytochrome P450 3A enzymes, such as [zileuton](#), should be avoided.

7) Probable Mechanism: inhibition by [zileuton](#) of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.1.HR| Ziprasidone

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

2) Summary: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [pimozide](#) with drugs that cause QT-interval prolongation is contraindicated, as coadministration may increase the risk of QT prolongation and serious [ventricular arrhythmias](#)[3].

7) Probable Mechanism: additive QT-interval prolongation

3.5.1.HS| Zotepine

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

2) Summary: Though no drug interaction studies have been performed, the manufacturer of [pimozide](#) states that coadministration [pimozide](#) with other drugs that potentially prolong the QTc interval is contraindicated[241]. Zotepine can prolong the QTc interval [242].

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of agents that prolong the QT interval, such as zotepine and [pimozide](#), is contraindicated.

7) Probable Mechanism: additive effects on QT prolongation

3.5.1.HT| Zuclopenthixol

- 1)) Interaction Effect: increased risk of QT prolongation
- 2)) Summary: Cases of QT prolongation, [ventricular arrhythmias](#) and fibrillation, [ventricular tachycardia](#), [torsade de pointes](#), and sudden death have been reported with zuclopenthixol[210][211] and therefore use is contraindicated with certain agents known to significantly increase the QT interval [1].
- 3)) Severity: contraindicated
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Cases of QT prolongation, [ventricular arrhythmias](#) and fibrillation, [ventricular tachycardia](#), [torsade de pointes](#), and sudden death have been reported with zuclopenthixol[210][211] and therefore use is contraindicated with certain agents known to significantly increase the QT interval [1].
- 7)) Probable Mechanism: additive QT prolongation

3.5.2] Drug-Food Combinations

3.5.2.A] Grapefruit Juice

- 1)) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2)) Summary: Grapefruit juice may inhibit the metabolism of [pimozide](#), resulting in increased serum concentrations of this agent. Elevated serum levels of [pimozide](#) have been associated with adverse cardiovascular effects including QT interval prolongation, [cardiac arrhythmia](#), and sudden death. The concurrent use of [pimozide](#) and grapefruit juice should be avoided[248].
- 3)) Severity: major
- 4)) Onset: rapid
- 5)) Substantiation: probable
- 6)) Clinical Management: Counsel patients to avoid grapefruit juice during [pimozide](#) therapy. Orange juice may be substituted as it provides the same basic nutrients but is not known to inhibit drug metabolism.
- 7)) Probable Mechanism: inhibition by grapefruit juice of cytochrome P450 3A-mediated [pimozide](#) metabolism

3.5.4] Drug-Tobacco Combinations

3.5.4.A] Tobacco

- 1)) Interaction Effect: decreased exposure of CYP1A2 substrates
- 2)) Summary: Cigarette smoking releases polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism[250][260], which may reduce CYP1A2 substrate bioavailability. Advise patients to stop smoking during treatment with a CYP1A2 substrate due to the potential reduction in efficacy [249]. If CYP1A2 substrate therapy is required in patients who smoke, consider monitoring for reduced efficacy [250] and adjusting the CYP1A2 substrate dosage if needed [251].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: CYP1A2 substrate bioavailability may be reduced with tobacco smoking. Advise patients to stop smoking during treatment due to the potential reduction in CYP1A2 substrate efficacy[249]. If therapy with a CYP1A2 substrate is required in patients who smoke, consider monitoring for reduced efficacy [250] and adjusting the CYP1A2 substrate dosage if needed [251].
- 7)) Probable Mechanism: induction of CYP1A2-mediated metabolism by tobacco smoke
- 8)) Literature Reports

a) Smoking 7 to 12 cigarettes/day produced maximum enzyme induction and a significantly lower mean [clozapine](#) concentration/dose (C/D) ratio in smokers than in nonsmokers (2.8 vs 6 nanograms/mL/mg/day), and similarly with [olanzapine](#) C/D ratio in another study (6.1 vs 12.8 nanograms/mL/mg/day). Smoking more than 12 cigarettes/day did not produce any further induction nor lower C/D ratio of [clozapine](#) or [olanzapine](#) [252].

b) Among patients treated with [mirtazapine](#) 30 mg/day for 4 weeks, smokers had significantly lower concentrations of S(+)-[mirtazapine](#) (23 vs 39 nmol/L) and [mirtazapine](#) S(+)/R(-) ratio (0.28 vs 0.37) than nonsmokers. These effects from smoking remained significant after multivariate analysis [251].

c) In patients receiving stable [clozapine](#) 100 mg/day, heavy smokers (30 or more cigarettes/day) had a significantly higher mean plasma [clozapine](#) concentration coefficient of variation (CV) than smokers (30% vs 16%); however, no difference was seen in patients receiving stable [clozapine](#) 300 or 600 mg/day in a study of patients with [schizophrenia](#) or [schizoaffective disorder](#) (N=47) [253].

d) In a study of patients receiving an average [clozapine](#) dose of 304 mg/day (N=18), [clozapine](#) and norclozapine (active metabolite) plasma concentrations were significantly lower in smokers (median of 25 cigarettes or 4 pipes/day) compared with nonsmokers. The [clozapine](#) plasma concentration in smokers was a significant 3.2-fold lower and norclozapine was 2.3-fold lower compared with plasma concentration in nonsmokers [254].

e) Induction of CYP1A2 activity by cigarette smoking significantly reduced [olanzapine](#) plasma concentrations and clinical effectiveness in smokers (10 to 40 cigarettes/day), compared with nonsmokers in a study of adults with thought disorder (N=17). After 15 days of [olanzapine](#) 10 mg/day, the dose-corrected steady-state [olanzapine](#) plasma concentration (C:D) ratio was about 5-fold lower in smokers compared with nonsmokers (1.56 vs 7.9 nanograms/mL/mg). At the same time, Brief Psychiatric Rating Scale total scores were significantly higher for nonsmokers than for smokers (30.4% vs 12.5%) and were positively correlated with the steady-state plasma [olanzapine](#) C:D ratio. Smoking induced a significant 6-fold higher level of CYP1A2 activity in smokers compared with nonsmokers and the index was closely correlated with the steady-state plasma [olanzapine](#) C:D ratio [255].

f) Cigarette smoking appears to release polycyclic aromatic hydrocarbons that induce CYP1A2 substrate metabolism. In vivo blood clearance and urine metabolite data from [caffeine](#) demethylation has clearly demonstrated the link between CYP1A2 activity and cigarette smoking, which may have clinical consequences when cigarette smoking occurs with [theophylline](#), [caffeine](#), [tacrine](#), [imipramine](#), [haloperidol](#), [pentazocine](#), [propranolol](#), or [flecainide](#) therapy [250].

g) In a study of healthy volunteers (N=14), chronically-exposed passive smokers had a significantly higher mean [theophylline](#) clearance of 60.1 mL/kg/hr compared with 40.9 mL/kg/hr for the nonsmokers. [256]. However, in another study of volunteers (N=5), intense, short-term (5 days) passive smoking did not effect [theophylline](#) disposition [257]. It was concluded that the short duration of exposure to tobacco smoke explained the lack of effect.

h) A retrospective study of patients with [schizophrenia](#) (N=50) revealed that cigarette smokers (more than 1 pack/day) had significantly lower plasma concentrations of [haloperidol](#) (16.83 vs 28.8 nanograms/mL) and reduced [haloperidol](#) (active metabolite; 16.76 vs 34.23 nanograms/mL) and significantly increased [haloperidol](#) oral clearance (1.58 vs 1.1 L/min) compared with nonsmokers [258].

- i) The administration of oral [imipramine](#) 3.5 mg/kg to smokers (15 cigarettes/day) resulted in significantly lower mean plasma levels of combined [imipramine](#) and desmethylinipramine when compared with nonsmokers (160 vs 290 nanograms/mL) [259].

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1] Monitoring Parameters

A) Therapeutic

1) Physical Findings

- a) Decrease in severity or elimination of target psychotic symptoms:

- 1) Positive psychotic symptoms (delusions, auditory hallucinations, racing thoughts)
- 2) Negative psychotic symptoms (anhedonia, apathy, amotivation, ambivalence).

- b) Improvement in socialization, grooming, and attention to activities of daily living.

B) Toxic

1) Physical Findings

- a) An ECG should be performed before initiation of [pimozide](#) therapy and periodically thereafter, especially during periods of dose adjustment. The QTc interval should not exceed 0.47 seconds in children or 0.52 seconds in adults, or more than 25% above the patient's original baseline [43].

- b) [Abnormal involuntary movement](#) scale (AIMS) examination or similar test for [tardive dyskinesia](#) every 6 months.

- c) Assessment for extrapyramidal symptoms (EPS) during dose adjustment and every 3 months.

4.2] Patient Instructions

A) [Pimozide](#) (By mouth)

[Pimozide](#)

Treats symptoms of [Tourette syndrome](#).

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use if you have had an [allergic reaction](#) to [pimozide](#), or if you have heart rhythm problems (such as [long QT syndrome](#)) or low potassium or magnesium blood levels.

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.

It is usually best to take this medicine at bedtime.

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.

You must avoid many other medicines while you are using [pimozide](#). These medicines used together could cause serious health problems, including death. Ask your doctor before you use any other medicine.

Tell your doctor if you are also using a macrolide antibiotic (such as [clarithromycin](#), [erythromycin](#), or [azithromycin](#)), medicine for depression (such as [citalopram](#), escitalopram, [sertraline](#), [nefazodone](#), [fluvoxamine](#), [fluoxetine](#)), medicine to treat a [fungus infection](#) (such as [itraconazole](#), [ketoconazole](#)), medicine to treat HIV/AIDS (such as [ritonavir](#), [saquinavir](#), [indinavir](#), [nelfinavir](#)), or [zileuton](#).

Some medicines and foods can affect how [pimozide](#) works. Tell your doctor if you also use medicine to treat seizures, a phenothiazine (such as [chlorpromazine](#), [perphenazine](#), [promethazine](#), [prochlorperazine](#), [thioridazine](#)), a tricyclic antidepressant (such as [amitriptyline](#)), medicine for heart rhythm problems (such as [dofetilide](#), [sotalol](#), [quinidine](#)), a diuretic (water pill), [pentamidine](#), [dolasetron](#), [tacrolimus](#), or [ziprasidone](#). Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Do not eat grapefruit or drink grapefruit juice while you are using this medicine.

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breastfeeding, or if you have [kidney disease](#), liver disease, [heart disease](#), or a history of seizures.

This medicine may cause the following problems:

- [Neuroleptic malignant syndrome](#) (a problem with the nervous system)

- [Tardive dyskinesia](#) (a movement disorder)

- Changes to your heartbeat

- Decreased numbers of blood cells, especially white blood cells

This medicine may make you drowsy or dizzy. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

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

- Chills, [cough](#), sore throat, and body aches

- Dizziness, fainting, lightheadedness

- Fast, slow, pounding, or uneven heartbeat

- Fever, sweating, confusion, muscle stiffness or spasms

- Problems with balance or walking

- New or ongoing muscle movement that you cannot control (often in your lips, tongue, jaw, arms, or legs)

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

Dry mouth

Sleepiness, weakness

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

4.3] Place In Therapy

A) **Pimozide's** primary place in therapy is in the treatment of **Tourette's syndrome** in patients who are refractory to **haloperidol** or who develop incapacitating side effects during **haloperidol** therapy [274].

B) Clinical studies have demonstrated no significant advantage of **pimozide** over other antipsychotic agents in the treatment of chronic schizophrenic patients [275]. The drug may find usefulness due to its long half-life, when given orally once weekly in **chronic schizophrenia** as an alternative to intramuscular **fluphenazine** decanoate given every 2 weeks. The drug should also be considered in patients where sedation is a problem with other antipsychotic agents. **Pimozide** may prove useful as an adjuvant to maintenance therapy with other antipsychotic agents in **chronic schizophrenia**. Also, **pimozide** may be effective in schizophrenic patients unresponsive to other antipsychotic medications.

C) Most controlled studies have indicated that **pimozide** is equally effective as other antipsychotic agents in the treatment of **chronic schizophrenia** [276][23][277][278][279][275]. However, there appears to be an advantage of **pimozide** over other agents in the treatment of patients with poor social adjustment with symptoms of emotional withdrawal, disturbed thought content, hallucinations and **blunted affect** [40]. **Pimozide** is less effective than the other antipsychotic agents, in general, for the excited, agitated chronic schizophrenic patient.

D) **Pimozide** is a useful addition to the formulary of institutions which handle **Tourette's syndrome** and other difficult-to-treat psychiatric patients.

4.4] Mechanism of Action / Pharmacology

A) Mechanism of Action

1) **Pimozide** is a potent antipsychotic drug, a diphenylbutylpiperidine derivative, structurally dissimilar from phenothiazines, butyrophenones, and thioxanthenes that elicits antipsychotic effects via central antidopaminergic activity [269][270][271]. The efficacy of **pimozide** in suppressing the tics of **Tourette's syndrome** is thought to be due to dopaminergic blockade. Secondary changes in central **dopamine** function and metabolism, including increased brain turnover of **dopamine**, may contribute to both the therapeutic and the adverse effects of **pimozide** [3].

2) **Pimozide** is thought to have more specific **dopamine** receptor blocking activity and less alpha-adrenergic receptor antagonism than other neuroleptic agents. This results in less potential for inducing sedation and hypotension. **Pimozide** also appears to block voltage-operated **calcium** channels and to interact with opiate receptors, probably as an antagonist [272].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] Gilles de la Tourette's syndrome, in patients who have failed to adequately respond to standard treatment

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; **Pediatric, yes (12 years and older)**

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; **Pediatric, Class IIa**

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

2) Summary:

Pimozide is indicated for the suppression of motor and phonic tics in adults and children 12 years of age and older with **Tourettes disorder** who have failed to adequately respond to standard treatment [3].

Pimozide is not intended for first line treatment or for tics which do not interfere with the patient's development and/or daily life functioning [3].

Effective in patients who were unable to tolerate or were unresponsive to **haloperidol** (Shapiro & Shapiro, 1984; Shapiro et al, 1983)

3) Adult:

a) The efficacy of **pimozide** for use in **Tourettes disorder** is based on 2 controlled clinical trials in patients between 8 and 53 years of age (most patients 12 years or older) [3].

b) **Haloperidol** has been the drug of choice in **Gilles de la Tourette syndrome**, its efficacy being related to **dopamine** receptor blocking activity in the CNS. **Pimozide** is a more specific antidopaminergic agent. Although effective, superiority of **pimozide** over **haloperidol** has not been adequately demonstrated [4]. The drug is indicated as reserve therapy for **Tourettes syndrome** in patients who have not responded to **haloperidol** or who cannot tolerate toxicity of **haloperidol**. A review of the efficacy and toxicity of **pimozide** in the treatment of tic and **Tourette disorders** is available [5].

c) In 9 patients with **Gilles de la Tourette syndrome** both **haloperidol** and **pimozide** were effective [6]. In this double-blind study, patients were assigned to **pimozide** or **haloperidol**, each in doses of 2 mg initially every morning, increasing by 2 mg every second day until symptoms disappeared or until side effects were observed or until maximum doses of 12 mg daily were obtained. A followup period of 420 months was undertaken. Both **pimozide** and **haloperidol** significantly reduced mean 5-minute tic counts, with no significant difference between the 2 drugs. Both **haloperidol** and **pimozide** were more effective than placebo. Followup at 4 to 20 months indicated that 6 of 7 patients continuing on **pimozide** and one of 2 patients continuing on **haloperidol** had a greater than 75% improvement in symptoms. Significantly fewer days of lethargy or tiredness was associated with **pimozide** than **haloperidol**. Anticholinergic and extrapyramidal effects were similar with both agents. **Pimozide** is an effective alternative to **haloperidol** in **Gilles de la Tourette syndrome**, particularly in **haloperidol** nonresponders or patients receiving **haloperidol** but developing incapacitating side effects.

4) Pediatric:

a) The efficacy of **pimozide** for use in **Tourettes disorder** is based on 2 controlled clinical trials in patients between 8 and 53 years of age (most patients 12 years or older) [3].

4.5.2] Non FDA Uses

4.5.2.A] Anorexia nervosa

1) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: Pediatric, **Class III**

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

Unclear efficacy

3) Pediatric:

a) All 10 adolescent anorectic females studied for a period of 20 weeks succeeded in gaining body weight with or without [pimozide](#) [7][8]. Five patients were treated by behavior therapy programs and the other 5 were treated with [pimozide](#). Serum prolactin levels were increased in the 5 patients receiving [pimozide](#), while no elevation was observed in patients undergoing behavior therapy.

b) One report has described the successful use of [pimozide](#) 4 milligrams orally 3 times daily for one month in [anorexia nervosa](#) in a 17-year-old male. Dramatic improvement was observed in 3 weeks with the patient gaining 9 kg. Obsession with weight disappeared at this time as well as bradycardia and overactivity [8].

4.5.2.B) Anxiety

1) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

as effective as [chlordiazepoxide](#) and [diazepam](#) in the treatment of non-psychotic patients with anxiety

However, offers no advantage over benzodiazepines

3) Adult:

a) [Pimozide](#) has been shown to be more effective than placebo in anxiety [27], and as effective as [haloperidol](#) [28]. [Pimozide](#) 2 milligrams daily has produced similar effects to [diazepam](#) 10 milligrams daily or [chlordiazepoxide](#) 40 milligrams daily [29][30].

b) The addition of [pimozide](#) 2 milligrams daily to [chlordiazepoxide](#) 30 to 60 milligrams daily did not result in a more rapid antianxiety effect, enhanced antianxiety effect or reduction of [chlordiazepoxide](#) dose, or a decrease in the incidence of side effects [31].

4.5.2.C) Chronic schizophrenia

1) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

2) Summary:

Efficacious in **chronic schizophrenia** (Kline et al, 1977; Donlon et al, 1977; Singh, 1971; Sugarman, 1971; Masheter, 1971; Arfwidsson et al, 1971)

Doses range from 2 to 40 milligrams (mean: 6 milligrams daily)

3) Adult:

a) **Pimozide** has been reported to be more specific than other antipsychotic agents for autistic patients with emotional withdrawal, delusions, and hallucinations as opposed to agitated or aggressive type patients with **chronic schizophrenia** [9][10]. **Pimozide** may have special usefulness, as opposed to other agents, in improving emotional withdrawal and assisting in resocialization of chronic schizophrenic patients [11][12][10][13][14]. However, at least one report has indicated that **pimozide** was no more effective than **chlorpromazine** in improving emotional withdrawal and social competence in **chronic schizophrenia** [15].

b) A significant improvement in negative symptoms, but not positive symptoms was observed with **pimozide** in schizophrenic patients [16]. The dose of **pimozide** was started at 4 milligrams/day and increased over 4 weeks to an average dose of 12.6 milligrams/day.

c) **Pimozide** given intermittently has proven effective in the management of **schizophrenia**, due to its long half-life [17][18]. The drug has been administered orally once weekly, producing equivalent clinical effects as that of **fluphenazine** decanoate administered once every 2 weeks [17].

d) **Pimozide** has been successful when used concurrently with maintenance antipsychotic medications on improving work behavior, work habits, and mental status in **chronic schizophrenics** following its addition to maintenance therapy (8 milligrams daily) [19]. The drug has been used successfully as replacement therapy in patients unresponsive to other neuroleptic agents, resulting in improvement in apathy and withdrawal in many patients who were unresponsive to other agents prior to **pimozide** therapy [20].

e) **Pimozide** in combination with other antipsychotic medications improved social behavior in **chronic schizophrenia** (Nakra et al, 1980). **Pimozide** was administered in oral doses of 8 milligrams daily for 12 weeks to 20 patients receiving other medications (**haloperidol**, flupenthixol, **trifluoperazines**, thiothixine, **fluphenazine**, promazine, or **chlorpromazine**). **Pimozide** significantly improved social behavior in terms of work behavior, work habits, and mental status after 8 weeks of treatment.

f) **Pimozide** was effective as single agent therapy for **chronic schizophrenia** in patients who were primarily withdrawn. Patients were administered **pimozide** 8 to 20 milligrams daily after withdrawal of all other medications for a period of one month. General improvement was observed after assessment at 4 and 6 months (Cheadle & Freedman, 1979). Marked improvement was reported in 6 of 12 patients with **chronic schizophrenia** undergoing acute exacerbations with **pimozide** in doses up to 16 milligrams daily over a period of 10 weeks. Patients demonstrated

improvement with thought disorders, apathy, emotional withdrawal, motor retardation and depression. This study supports the antiautistic and antidelusional effects of [pimozide](#) [21].

4.5.2.D] [Huntington's disease](#)

1) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

Effective in the treatment of [Huntington's chorea](#) (Siegmund et al, 1982; Fog & Pakkenberg, 1970)

3) Adult:

a) Oral [pimozide](#) 16 milligrams daily (in 3 to 4 divided doses; maximum 40 milligrams daily) produced good long-term results in 9 of 11 patients with [Huntington's chorea](#), with significant improvement in hyperkinesia. These patients were discharged from the hospital indicating therapy may permit social reintegration and improved quality of life for Huntington's patients. However, both [haloperidol](#) and [chlorpromazine](#) have been utilized with some degree of success in [Huntington's chorea](#) [9] and controlled studies are required to determine any benefits of [pimozide](#).

4.5.2.E] [Obsessive-compulsive disorder](#)

1) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2) Summary:

Useful in treating some subtypes of [obsessive compulsive disorder](#)

3) Adult:

a) The addition of [pimozide](#) was useful in treating a possible subtype of [obsessive compulsive disorder](#) (OCD) in a patient with a dual diagnosis of OCD and chronic multiple tics or [Tourette's Syndrome](#). A 25-year-old man with a history of [Tourette's Syndrome](#) presented for treatment of OCD symptoms [32]. [Fluvoxamine](#) alone appeared to exacerbate tics leading to the onset of coprolalia, without improving OCD symptoms. [Pimozide](#) alone reduced tics very slightly. In this patient, the combination of [fluvoxamine](#) (150 to 250 milligram/day) and [pimozide](#) (1 milligram/day) appeared to be necessary for clinical improvement of OCD symptoms, suggesting that both

the [dopamine](#) and serotonin systems were involved in the near remission of OCD symptoms and the reduction of tics.

b)) [Pimozide](#) was used successfully for 7 months in [onychotillomania](#). The condition was reported to be a manifestation of [obsessive compulsive disorder](#) [33].

4.5.2.F) [Trigeminal trophic syndrome](#)

1)) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2)) Summary:

In one case, successfully treated severe trigeminal neurotrophic [ulceration](#)

3)) Adult:

a)) A rare case was described of an 82-year-old woman with severe trigeminal neurotrophic [ulceration](#) which improved substantially with [pimozide](#), given for treatment of unrelated paranoid symptoms. The established use of [pimozide](#) in delusional [parasitosis](#) in relationship to this case was discussed [34].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] [Chlorpromazine](#)

4.6.A.1] [Mania](#)

a)) SUMMARY: [Pimozide](#) is at least as effective as [chlorproMAZINE](#) in the treatment of mania [290] [291][292]. In a double-blind, randomized fashion, 23 mania patients received either [pimozide](#) 2 milligrams (mg) or [chlorproMAZINE](#) 100 milligrams (mg), with adjustments to a maximum of 32 mg/day and 1600 mg/day, respectively. The patients were evaluated for 14 days using two scales, the Mania Rating Scale (MRS) and the Petterson Rating Scale (PRS). MRS evaluation demonstrated [chlorproMAZINE](#) to be more effective than [pimozide](#), probable due to greater sedative effects [291].

4.6.A.2] [Schizophrenia](#)

a)) Similar clinical effects were reported with [pimozide](#) (mean dose, 7 milligrams (mg) daily) and [chlorproMAZINE](#) sustained-release (mean dose, 216 mg daily) in the treatment of [chronic schizophrenia](#) [293]. Similar results were observed in chronic schizophrenic patients in a double-blind study over 52 weeks [294]. Average daily doses of [pimozide](#) 7.3 mg were as effective as [chlorproMAZINE](#) 381 mg. There was no significant difference in improvement or side effects between the two drug treatment groups except for a higher incidence of skin reactions with [chlorproMAZINE](#). However, the authors were unable to replicate previous data indicating the special utility of [pimozide](#) for improvement of emotional withdrawal and social competence in [schizophrenia](#) in this long-term study. All patients in this study were stable, compliant patients which may not be the optimal group for the evaluation of these effects.

4.6.B] Fluphenazine

4.6.B.1] Schizophrenia

- a) SUMMARY: Clinical studies have reported the equivalent effects of fluphenazine and pimozide in chronic schizophrenia [280][281][282][283][284][285][286].
- b) The comparative efficacy of fluphenazine HCl (12.5 milligrams daily, average) and pimozide (9.6 milligrams daily, average) were reported in the treatment of chronic schizophrenia in a 12-month study. Both drugs were equally effective in maintaining control of symptomatology at a better level than previous medication [284].
- c) Other reports have reported the comparability of long-acting fluphenazine and pimozide. There was equivalent efficacy with fluphenazine decanoate given biweekly and pimozide 4 days each week [287]. In a subsequent report, pimozide once weekly (in doses up to 60 milligrams) and fluphenazine decanoate (up to 50 milligrams every 2 weeks) were equally effective in the management of chronic schizophrenia [288]. Tardive dyskinesia was more frequent in pimozide patients. Pimozide may be considered an alternative to intramuscular fluphenazine for chronic schizophrenia.
- d) Depot fluphenazine decanoate and oral pimozide were compared in 36 schizophrenic outpatients over 1 year in a double-blind, placebo-controlled trial. Analyses of Social Behavior Assessment Schedule (SBAS) data from pre-trial and end of study assessments revealed no significant advantage for either of the treatments [289].

4.6.C] Haloperidol

4.6.C.1] Gilles de la Tourette's syndrome

- a) The efficacy of pimozide in Tourette's syndrome was evaluated [305]. Although effective, superiority of the drug over haloperidol has not been adequately demonstrated. The drug is indicated as reserve therapy for Tourette's syndrome in patients who have not responded to haloperidol or who cannot tolerate toxicity of haloperidol.
- b) In a 6-month, controlled crossover trial of children and adolescents (n=22) with Tourette's syndrome, only pimozide demonstrated statistical improvement over placebo on the global rating scale (p less than 0.05). However, pimozide and haloperidol did not differ statistically in efficacy from each other. Overall, 64% of subjects attained the goal of 70% tic reduction with active therapy as compared to only 23% with placebo. The mean effective doses of pimozide and haloperidol were equivalent (3.4 and 3.5 milligrams daily, respectively). Haloperidol was associated with a greater incidence of extrapyramidal symptoms [306].
- c) Haloperidol was compared with pimozide in 9 patients with Gilles de la Tourette syndrome [307]. In this double-blind study, patients were assigned to pimozide or haloperidol, each in doses of 2 milligrams (mg) initially every morning, increasing by 2 mg every second day until symptoms disappeared or until side effects were observed or until maximum doses of 12 mg daily were obtained. A follow-up period of 420 months was undertaken. Both pimozide and haloperidol significantly reduced mean 5-minute tic counts, with no significant difference between the 2 drugs. Both haloperidol and pimozide were more effective than placebo. Follow-up at 4 to 20 months indicated that 6 of 7 patients continuing on pimozide and one of 2 patients continuing on haloperidol had a greater than 75% improvement in symptoms. Significantly fewer days of lethargy or tiredness was associated with pimozide than haloperidol. Anticholinergic and extrapyramidal effects were similar with both agents. Pimozide may be an effective alternative to haloperidol in Gilles de la Tourette syndrome, particularly in haloperidol non-responders or patients receiving haloperidol but developing incapacitating side effects.
- d) Haloperidol was compared with pimozide in a double-blind, parallel, crossover study lasting 6 weeks in 57 patients with Tourette's syndrome. The maximum dose of haloperidol was 10 milligrams (mg)/day, and

for **pimozide** it was 20 mg/day. **Haloperidol** was slightly more effective than **pimozide** in the treatment of **Tourette's syndrome**. Adverse effects of **haloperidol** were not significantly different than those of **pimozide**. Clinically significant cardiac effects did not occur. However, due to the potential of **pimozide** prolonging QTC intervals, **haloperidol** is the drug of choice for initial treatment of **Tourette's syndrome** [308].

4.6.C.2] Schizophrenia

- a) SUMMARY: **Pimozide** is at least as effective as **haloperidol** in the treatment of **chronic schizophrenia**.
- b) **Pimozide** was compared with **haloperidol** (5 to 50 milligrams/day (mg/day) of either) in relation to dopaminergic blockade and clinical response in 22 patients with **schizophrenia**. The drugs were equally effective. There was no correlation between either dopaminergic blockade or blood level and therapeutic response [302].
- c) **Pimozide** 306 mg daily was superior to **haloperidol** 7 to 14 mg daily in **chronic schizophrenia** in a small double-blind study. A subsequent report has indicated the equivalent efficacy of **pimozide** 10 to 60 mg daily and **haloperidol** 10 to 60 mg daily in acute **schizophrenia** [303]. In this study, however, extrapyramidal effects were more pronounced in patients using **pimozide** [304].

4.6.D] Levosulpiride

4.6.D.1] Schizophrenia

- a) A single-blind, randomized clinical study compared the therapeutic efficacy of levosulpiride and **pimozide** in the treatment of schizophrenic patients with negative symptoms not relieved by **haloperidol**. Following Andreasen's diagnostic criteria based on the Scale of Assessment of Positive Symptoms and the Scale of Assessment of Negative Symptoms, the study showed that the therapeutic activity of low doses of levosulpiride (200 milligrams/day (mg/day) orally) was higher than **pimozide** 4 mg/day orally [301].

4.6.E] Trifluoperazine

4.6.E.1] Schizophrenia

- a) Comparative studies have reported the similarity of **trifluoperazine** (5 to 30 milligrams daily) and **pimozide** (2 to 80 milligrams daily) in the management of **chronic schizophrenia** [295][296]. Other reports have indicated the superiority of **pimozide** over **trifluoperazine** for retardation, emotional withdrawal and unusual thought content in **chronic schizophrenia** [297][298][299]. A more recent report has confirmed these observations [300], with **pimozide** being reported superior to **trifluoperazine** in improving anxiety, motor retardation, suspiciousness and emotional adjustment, indicating its preferability in certain apathic schizophrenic patients.

6.0] References

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- 422 Product Information: Starlix(R) oral tablets, nateglinide oral tablets. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2011.
- 423 Product Information: VIRACEPT(R) oral tablets, oral powder for solution, nelfinavir mesylate oral tablets, oral powder for solution. ViiV Healthcare Company (per FDA), Research Triangle Park, NC, 2015.
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