PRODUCT MONOGRAPH

[Pr] PIMOZIDE

Pimozide Tablets USP

2 mg and 4 mg

Antipsychotic

AA PHARMA INC.
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[PR] PIMOZIDE

Pimozide Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets: 2 mg, 4 mg	Anhydrous Lactose, Croscarmellose Sodium, Magnesium Stearate 4 mg Tablets: contains additional D & C Yellow #10 Aluminium Lake 14-18%, Indigotine AL Lake 12-14% (Blue #2)

INDICATIONS AND CLINICAL USE

PIMOZIDE is indicated in the management of the manifestations of chronic schizophrenia in which the main manifestations do not include excitement, agitation or hyperactivity.

Pimozide has relatively little sedative action and can be used as a once-daily medication.

Pimozide is not indicated in the management of patients with mania or acute schizophrenia.

Geriatrics (≥*65* years of age):
Pimozide is not indicated in elderly patients with dementia. The safety and efficacy of pimozide in patients 65 years of age or older have not been studied (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box, and Special Populations).

Pediatrics (<18 years of age):
The safety and efficacy of pimozide in children under the age of 18 have not been studied.

CONTRAINDICATIONS

PIMOZIDE is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

- Central nervous system depression, brain damage, comatose states, liver disorders, renal insufficiency, pheochromocytoma and blood dyscrasias. It should not be used in depressive disorders or Parkinson's syndrome.

- Patients with congenital long QT syndrome or with a family history of this syndrome and in patients with a history of cardiac arrhythmias or Torsade de Pointes. A pre-treatment ECG is thus recommended to exclude these conditions. Pimozide should not be used in the case of acquired long QT interval, such as associated with concomitant use of drugs known to prolong the QT interval (see DRUG INTERACTIONS), known hypokalemia or hypomagnesemia, or clinically significant bradycardia.

- Combination with CYP 3A4-inhibiting drugs (such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone) or CYP 2D6-inhibiting drugs (such as quinidine). The inhibition of either or both enzymes (CYP 3A4 and CYP 2D6) of the cytochrome P450 systems may result in the elevation of pimozide blood concentration and increase the possibility of QT-prolongation (see DRUG INTERACTIONS).

- The treatment of simple tics or tics other than those associated with Tourette's Disorder.

- Combination with serotonin reuptake inhibitors, such as, sertraline, paroxetine, citalopram and escitalopram (see DRUG INTERACTIONS).

- A scheduled regional or spinal anesthesia.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia:
Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6 fold increase in death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature (see WARNINGS AND PRECAUTIONS, Special Populations, Use in Geriatric Patients with Dementia).

General

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Hyperpyrexia has been reported with other antipsychotic drugs. Appropriate care is advised when prescribing Pimozide to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity or being subject to dehydration.

Cardiovascular

There have been very rare reports of QT prolongation, ventricular arrhythmias, and Torsade de Pointes in patients without risk factors for QT prolongation administered therapeutic doses of pimozide, and in the setting of overdose. Ventricular tachycardia and ventricular fibrillation (in some cases with fatal outcomes) have also been reported, in addition to very rare reports of sudden death and cardiac arrest.

As with other neuroleptics, cases of sudden, unexpected deaths have been reported with pimozide, at recommended doses and in the setting of overdoses.

Many drugs that cause QT/QTc prolongation are suspected to increase the risk of Torsade de Pointes. Generally, the risk of Torsade de Pointes increases with the magnitude of QT/QTc prolongation produced by the drug. Torsade de Pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

An ECG should be performed prior to initiation of treatment with pimozide, as well as periodically during treatment (although there is no proof that periodic ECG monitoring will reduce the risk of Torsade de Pointes). If repolarization changes (prolongation of QT interval, T-wave changes or U-wave development) appear or arrhythmias develop, the need for treatment with pimozide in these patients should be reviewed. They should be closely monitored and their dose of pimozide should be reduced or the drug discontinued. If QT or QTc exceeds 500 msec, pimozide should be discontinued.

Particular care should be exercised when administering pimozide or its use avoided in patients who are suspected to be at an increased risk of experiencing Torsade de Pointes during treatment with a QT/QTc-prolonging drug. Risk factors for Torsade de Pointes in the general population include, but are not limited to, the following:

- female
- age 65 years or older
- baseline prolongation of the QT/QTc interval
- presence of genetic variants affecting cardiac ion channels or
- regulatory proteins, especially congenital long QT syndromes
- family history of QT prolongation, or sudden cardiac death at <50 years
- cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease)
- history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation)
- electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- bradycardia (<50 beats per minute)
- acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma)
- nutritional deficits (e.g., eating disorders, extreme diets)
- diabetes mellitus
- autonomic neuropathy

- hepatic dysfunction, renal dysfunction, and/or phenotypic/genotypic poor metabolizers of drug metabolizing enzyme isoforms, if relevant to the elimination of the drug.

Physicians who prescribe drugs that prolong the QT/QTc interval should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Potential for Hypotension: Hypotension may very rarely occur. Patients receiving pimozide should be observed for evidence of hypotension. Some individuals, especially the elderly or debilitated, have demonstrated transient hypotension for several hours following drug administration.

Endocrine and Metabolism

Hormonal effects of antipsychotic/neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia, oligomenorrhoea or amenorrhoea, and erectile dysfunction.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. The clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies, nor epidemiological studies conducted to date, have shown an association between chronic administration of these drugs and mammary tumorogenesis; the available evidence is considered too limited to be conclusive at this time.

Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Hyperglycemia: Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Gastrointestinal

Antiemetic Effects: As with other antipsychotics, pimozide has a substantial antiemetic effect. Thus, caution should be exercised in cases where the suppression of nausea and vomiting might hinder the diagnosis of an underlying physical disorder.

Genitourinary

Rare cases of priapism have been reported with antipsychotic use, such as pimozide. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic
Neutropenia, leukopenia, granulocytopenia, agranulocytosis and anemia have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting pimozide, and then periodically throughout treatment.

Venous thromboembolism (VTE)
VTE, including fatal pulmonary embolism, has been reported with antipsychotic drugs, including pimozide, in case reports and/or observational studies. When prescribing pimozide, all potential risk factors for VTE should be identified and preventative measures undertaken.

Hepatic/Biliary/Pancreatic
Caution is advised in patients with liver disease because pimozide is metabolized in the liver.

Neurologic
Increased Psychomotor Activity: Clinical trials with pimozide indicate that it is not effective in, and therefore should not be used in the management of manifestations of chronic schizophrenia in which the main symptoms include agitation, excitement and anxiety.

Neuroleptic Malignant Syndrome: In common with other antipsychotic drugs, pimozide has been associated with neuroleptic malignant syndrome: an idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, and altered consciousness. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described above under 'Tardive Dyskinesia' except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but, until further evidence becomes available, it seems reasonable to gradually withdraw use of antipsychotic drugs.

In schizophrenia, the response to antipsychotic drug treatment may be delayed. If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months. Acute withdrawal symptoms, including nausea, vomiting, transient dyskinetic signs, and insomnia, have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Gradual withdrawal is advisable.

Seizures: As with other antipsychotic drugs, pimozide should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. In addition, grand mal convulsions have been reported in association with pimozide.

Extrapyramidal Symptoms: In common with all neuroleptics, extrapyramidal symptoms may occur (see ADVERSE REACTIONS).

Anticonvulsants: Since pimozide may lower the convulsive threshold, it should be used with caution in epileptic patients and adequate anticonvulsive medication should be maintained.

Effects on Driving Ability and Use of Machinery: Pimozide may impair alertness, especially at the start of treatment. These effects may be potentiated by alcohol. Patients should be warned of the risks of sedation and advised not to drive or operate machinery during treatment until their susceptibility is known.

Special Populations

Pregnant Women:
The safety of pimozide in pregnancy has not been studied. Therefore, it should not be administered to women of child-bearing potential, particularly during the first trimester of pregnancy, unless, in the opinion of the physician, the expected benefits of the drug to the patient outweigh the potential risk to the fetus or child.

Teratogenic Effects: Teratogenic effects have not been observed.

Non-Teratogenic Effects: Animal data have shown some embryo-toxicity at dose level similar to the maximum human use level (MHUL). In addition, fetal growth retardation and fetal-toxicity was observed at dose levels of approximately 6 times the MHUL on an mg/kg basis. Neonates exposed to antipsychotic drugs (including pimozide) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases, neonates have required intensive care unit support and prolonged hospitalization.

Nursing Women:
Pimozide may be excreted in breast milk. If the use of pimozide tablets is considered essential, breast feeding should be discontinued.

Pediatrics (<18 years of age):
Safety and effectiveness in children have not been established, therefore, this drug is not recommended for use in the pediatric age group.

Geriatrics (≥65 years of age):
The safety and efficacy of pimozide in patients 65 years of age or older have not been studied.

Caution should be exercised with the use of pimozide in the elderly patient, recognizing the more frequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication in this population. (see DOSAGE AND ADMINISTRATION).

Use in Geriatric Patients with Dementia
Pimozide is not indicated in elderly patients with dementia. Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a metaanalysis of 13 controlled trials of various atypical antipsychotic drugs.

ADVERSE REACTIONS

Post-Market Adverse Drug Reactions
The following serious and unexpected adverse events have been reported. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: blood dyscrasias* (agranulocytosis, anemia, aplastic anemia, eosinophilia, granulocytopenia, leukopenia, neutropenia, pancytopenia, thrombocytopenic purpura), bone marrow failure, disseminated intravascular coagulation, leukocytosis, lymphadenopathy, polycythaemia, thrombocytopenia.
* It is recommended that patients have their complete blood count (CBC) tested prior to starting pimozide and then periodically throughout treatment.

Cardiac Disorders: angina pectoris, arrhythmia, coronary atherosclerosis, atrioventricular block, cardiac arrest, cardiac failure, cardiac valve disease, cardio-respiratory arrest, cardiomegaly, coronary artery disease, myocardial infarction, myocardial ischemia, myocarditis, stress cardiomyopathy, torsade de pointes, ventricular tachycardia, ventricular fibrillation.

Congenital, Familial and Genetic Disorders: congenital anomaly, congenital hydronephrosis, double ureter, dysmorphism, macrocephaly, microphthalmos, skull malformation, Tourette's disorder, urinary tract malformation, ventricular septal defect.

Endocrine Disorder: increased blood prolactin, hyperglycemia (in patients with pre-existing diabetes), hyperprolactinemia, hyperthyroidism, inappropriate antidiuretic hormone secretion.

Eye Disorder: accommodation disorder, glaucoma, oculogyration, blurred vision, visual impairment.

Gastrointestinal Disorders: constipation**, diarrhea, dry mouth, haemorrhagic enterocolitis, fecal incontinence, intestinal ischemia, pancreatitis, salivary hypersecretion, subileus, vomiting.

**Patients should be advised of the risk of severe constipation during pimozide treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

General Disorder and Administration Site Conditions: asthenia, death, drug interaction, face oedema, fatigue, hyperthermia, hypothermia, macrosomia, malaise, pyrexia.

Hepatobiliary Disorders: abnormal hepatic function, hepatitis, hepatomegaly, liver injury.

Immune System Disorders: antiphospholipid syndrome.

Infections and Infestations: bacterial infection, bacterial toxaemia, bronchitis, bronchopneumonia, pneumonia, pustular rash.

Injury, Poisoning and Procedural Complications: accidental exposure, contusion, drug dispensing error, drug toxicity, fall, femoral neck fracture, overdose, wound.

Investigations: increased blood creatinine phosphokinase, increased blood phosphorus, decreased blood pressure, increased blood pressure, breath sounds, circulating coagulant, increased drug level, abnormal electrocardiogram (repolarisation, ST segment depression, T wave inversion, T wave peaked), prolonged electrocardiogram QT interval, abnormal electroencephalogram, decreased hematocrit, decreased haemoglobin, increased hepatic enzyme, decreased red blood cell count, increased red cell distribution width, increased respiratory rate, increased transaminases, increased weight, decreased white blood cell count, increased white blood cell count.

Metabolism and Nutrition Disorders: decreased appetite, diabetes mellitus (type I and type II), dyslipidaemia, reduced fluid intake, hyperphagia, hypoglycaemia, hypokalaemia, hyponatraemia, ketoacidosis.

Musculoskeletal and Connective Tissue Disorders: arthralgia, muscle rigidity, myalgia, nuchal rigidity, rhabdomyolysis, soft tissue haemorrhage, systemic lupus erythematosus.

*Benign, Malignant and Unspecified Neoplasms (Including Cysts and Polyps)***:** endometrial cancer, myelodysplastic syndrome.

Nervous System Disorders: akathisia, altered state of consciousness, bradykinesia, cognitive disorder, cogwheel rigidity, coma, convulsion, dementia, disturbance in attention, dizziness, drooling, dyskinesia, dystonia, epilepsy, extrapyramidal disorder, grand mal convulsion, haemorrhagic cerebral infarction, headache, hypoaesthesia, hypokinesia, hypoxic-ischemic encephalopathy, loss of consciousness (syncope), lethargy, masked facies, mental retardation, neuroleptic malignant syndrome, parkinsonism, somnolence, stupor, tardive dyskinesia, tremor, unresponsive to stimuli.

Pregnancy, Puerperium and Prenatal Conditions: missed abortion, spontaneous abortion.

Psychiatric Disorder: abnormal behaviour, aggression, agitation, apathy, confusional state, decreased activity, delusion, depression, disorientation, drug dependence, euphoric mood, hallucination, insomnia, decreased libido, mutism, psychomotor retardation, restlessness, schizophrenia, self injurious behaviour, sleep disorder, suicide, suicide attempt, withdrawal syndrome.

Renal and Urinary Disorders: anuria, glycosuria, haematuria, nephrotic syndrome, renal failure, urinary incontinence, urinary retention**.**

Reproductive System and Breast Disorder: amenorrhoea, breast cysts, erectile dysfunction, galactorrhoea, gynaecomastia.

Respiratory, Thoracic and Mediastinal Disorders: asphyxia, bradypnoea, dyspnoea, hypoxia, lung disorder, oropharyngeal spasm, pulmonary congestion, pulmonary embolism, pulmonary oedema, pulmonary thrombosis, respiratory arrest.

Skin and Subcutaneous Tissue Disorders: angioedema, hyperhidrosis, photosensitivity reaction, pruritus, rash (exfoliative, erythematous, popular), skin exfoliation, skin toxicity, toxic skin eruption, urticarial.

Vascular Disorders: arteriosclerosis, circulatory collapse, deep vein thrombosis, venous embolism, hematoma, hypertension (orthostatic), phlebitis, shock, thrombosis.

DRUG INTERACTIONS

Overview

CNS
Potentiation of the effects of drugs acting on the central nervous system (anesthetics, opiates, alcohol, etc.) as well as atropine and organophosphorous insecticides may occur with the use of pimozide. Both animal and human data indicate that pimozide may block the action of amphetamines. Therefore, concomitant use of the two medications is not recommended.

Levodopa
Pimozide may, in a dose-related way, impair the antiparkinson effect of levodopa.

Antihypertensives
Concomitant administration of antihypertensive agents should be undertaken with caution in view of the fact that other antipsychotics, notably the phenothiazines, have blocked the action of these agents.

Drugs That Inhibit Cytochrome P450
Pimozide is metabolized mainly via the cytochrome P450 subtype 3A4 (CYP 3A4) enzyme system and more discreetly via the CYP 2D6 subtype. *In vitro* data indicate that especially potent inhibitors of CYP 3A4 enzyme system, such as aprepitant, azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone will inhibit the metabolism of pimozide, resulting in markedly elevated plasma levels of pimozide. *In vitro* data also indicate that quinidine diminishes the CYP 2D6 dependent metabolism of pimozide. Elevated pimozide levels may enhance the risk of QT prolongation.

As CYP 1A2 may also contribute to the metabolism of pimozide tablets, prescribers should be aware of the theoretical potential for drug interactions with inhibitors of this enzymatic system.

Drugs That Prolong QT Interval
Concomitant use of pimozide with drugs known to prolong the QT interval are contraindicated (see CONTRAINDICATIONS).

Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol)
- antidepressants (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants)
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin)
- quinolone antibiotics (e.g., moxifloxacin, gatifloxacin)
- pentamidine
- antimalarials (e.g., quinine)
- azole antifungals (e.g., fluconazole, itraconazole**,** ketoconazole, voriconazole)
- domperidone
- 5-HT_3 antagonists (e.g., dolasetron, ondansetron)
- tacrolimus
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Particular care should be taken to avoid toxic plasma levels of lithium when this agent is administered together with pimozide, since such toxic levels have also been associated with QT prolongation.

Do not administer in combination with drugs causing electrolyte alteration. Concomitant use with diuretics should be avoided, in particular those causing hypokalemia. Other drugs that can disrupt electrolyte levels, include, but are not limited to, the followings:

- laxatives and enemas
- amphotericin B
- high dose corticosteroids

SSRI (Selective Serotonin Reuptake Inhibitor) Antidepressants:
An *in vivo* study of pimozide added to steady state sertraline revealed a 40% increase in the pimozide AUC and C_{max} (see CONTRAINDICATIONS).

An *in vivo* study of co-administered pimozide and citalopram resulted in a mean increase of QTc values of approximately 10 milliseconds. Citalopram did not alter the AUC and C_{max} of pimozide (see CONTRAINDICATIONS).

An *in vivo* study of co-administered pimozide (a single 2 mg dose) and paroxetine (60 mg daily) was associated with mean increases of 151% in pimozide AUC and 62% in pimozide C_{max} (see CONTRAINDICATIONS).

Drug-Food Interactions

Grapefruit Juice
As grapefruit juice is known to inhibit the metabolism of CYP 3A4 metabolized drugs, concomitant use of grapefruit juice with ORAP® tablets should be avoided.

Drug-Herb Interactions

Betel Nut
Concurrent use of Betel nut may result in an increased risk of extrapyramidal side effects of pimozide.

Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking fluphenazine and fluphenthixol for schizophrenia. The extrapyramidal effects were not improved with anticholinergic therapy with procyclidine, and resolved with betel nut discontinuation.

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. Case reports suggest the onset of betel nut activity to be within 2 weeks with resolution within 4 to 7 days after discontinuation.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Geriatrics: **Pimozide is not indicated in elderly patients with dementia.** The safety and efficacy of pimozide in patients 65 years of age or older have not been studied **(see WARNINGS AND PRECAUTIONS).**

Given the higher incidence of concomitant illness (renal, hepatic and cardiovascular) and concomitant medication in the elderly, pimozide should be used with caution in this population. It is recommended that treatment be started with half of the adult starting dose.

Recommended Dose and Dosage Adjustment
A single morning dose is recommended for all patients.

Adults
Usual Starting Dose: The initial recommended dose in patients with chronic schizophrenia for whom pimozide might be indicated is 2 to 4 mg once daily, with weekly increments of 2 to 4 mg until a satisfactory level of therapeutic effect is attained or excessive adverse effects occur.

Maintenance Therapy: The average maintenance dose is 6 mg daily with the usual range of 2 to 12 mg per day. Daily doses above 20 mg are not recommended.

The patients should be reviewed regularly to ensure the minimum effective dose is being used.

Missed Dose
If a patient misses a dose, advise the patient to take the dose as soon as possible and continue with their regular schedule. If it is almost time for the next dose, advise the patient to skip the missed dose and continue with the next scheduled dose. Advise patients not to take 2 doses of Pimozide at the same time to make up for a missed dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Symptoms
In general, the signs and symptoms of overdosage with pimozide would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be extrapyramidal symptoms. The risk of cardiac arrhythmias, possibly associated with QT prolongation and ventricular arrhythmias including Torsade de Pointes should be considered. If these arrhythmias are severe, they can be associated with hypotension and circulatory collapse.

Treatment
There is no specific antidote for pimozide. In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary, mechanically-assisted respiration are advised. Continuous electrocardiographic monitoring should be performed due to risk of QT interval prolongation and ventricular arrhythmias including Torsade de Pointes and continued until the ECG parameters are within the normal range. Severe arrhythmias should be treated with appropriate antiarrhythmic treatment. Associated hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as dopamine or dobutamine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pimozide is a diphenylbutylpiperidine derivative with neuroleptic properties that has been found to be useful in the management of chronic schizophrenic patients. It is relatively non-sedating and can be administered in a single daily dosage.

It is assumed that the basic mechanism of action of pimozide is related to its action on central aminergic receptors. It appears to have a selective ability to block central dopaminergic receptors, although it affects noradrenaline turnover at higher doses. The extrapyramidal effects typical of other neuroleptic agents are seen also with pimozide, but it appears to have fewer autonomic effects. As with other neuroleptics, endocrine effects and ECG changes have also been reported with pimozide.

Pharmacokinetics

Absorption: More than 50% of a dose of pimozide is absorbed after oral administration. Peak serum levels occur generally six to eight hours (range: 4-12 hours) after dosing.

Metabolism: Pimozide appears to undergo significant first-pass metabolism. Pimozide is extensively metabolized, primarily by N-dealkylation in the liver. Two major metabolites have been identified: 1-(4-piperidyl)-2-benzimidazolinone and 4,4-bis(4-fluorphenyl) butyric acid. These metabolites have no antipsychotic activity.

The mean elimination half-life of pimozide in schizophrenic patients was approximately 55 hours. There was a more than ten-fold interindividual difference in the area under the serum pimozide level time curve and an equivalent degree of variation in peak serum levels among patients studied. The significance of this is unclear, since there are few correlations between plasma levels and clinical findings.

Excretion: Only a very small fraction of pimozide is excreted unchanged in the urine. The major route of elimination of the metabolites is through the kidney.

STABILITY AND STORAGE RECOMMENDATIONS

Store at controlled room temperature (15 to 30°C) in tight containers.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PIMOZIDE 2 mg Tablets: Each round, white tablet scored and engraved “PIM” over “2” on one side, contains 2 mg of pimozide. Available in bottles of 100 tablets.

PIMOZIDE 4 mg Tablets: Each round, light green tablet scored and engraved “PIM” over “4” on one side, contains 4 mg of pimozide. Available in bottles of 100 tablets.

Each tablet contains the following nonmedicinal ingredient: anhydrous lactose, croscarmellose sodium and magnesium stearate. The 4 mg tablet contain additional D & C Yellow #10 Aluminium Lake 14-18% and Indigotine AL Lake 12-14% (Blue #2).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

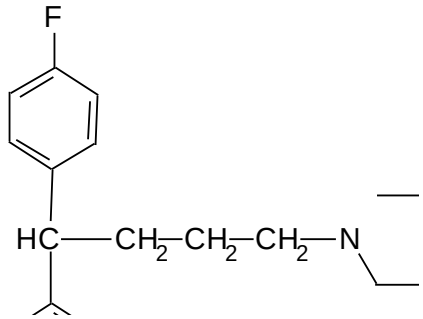
Trade Name: PIMOZIDE

Proper Name: Pimozide

Chemical Names:
1) 1-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidizole-2-one
2) 1-[1-[4,4-Bis(p-fluorophenyl)butyl]-4-piperidinyl]-2-benzimidizolinone

Molecular Formula: $C_{28}H_{29}F_2N_3O$

Structural Formula:



Molecular Weight: 461.6

Description: A white, or almost white, powder.

CLINICAL TRIALS

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of pimozide was measured and compared following oral administration of a 4 mg dose of PIMOZIDE 4 mg tablets or ORAP® (pimozide) 4 mg tablets, under fasted conditions. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data
Pimozide
(A single 4 mg dose: 1 x 4 mg)
From Measured Data/Fasted Conditions
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test*	Reference†	Ratio of Geometric Means (%)#	90% Confidence Interval (%)
AUC_{0-72} (ng•h/mL)	62.1 70.6 (64)	58.7 66.7 (61)	105.9	98.7 – 113.7
AUC_I (ng•h/mL)	73.1 84.8 (68)	68.9 80.1 (67)	106.2	98.6 – 114.4
C_{max} (ng/mL)	2.29 2.50 (49)	2.11 2.31 (49)	108.1	100.5 – 116.3
T_{max}§ (h)	6.41 (22)	6.96 (38)		
$t_{1/2}$§ (h)	25.4 (21)	25.2 (19)		

* Pimozide 4 mg tablets (AA Pharma Inc.)
† Orap® (pimozide) 4 mg tablets (Janssen-Ortho Inc.) was purchased in Canada.
# Based on the least square estimate.
§ Expressed as arithmetic means (CV%) only.

DETAILED PHARMACOLOGY

Animals

The pharmacological profile of pimozide in laboratory animals resembles that of other antipsychotics.

As with other neuroleptics, pimozide reduces locomotor and exploratory behaviour at low doses, and induces catatonic immobility and palpebral ptosis in rats at higher doses.
Pimozide inhibits conditioned avoidance responding in rats and dogs and self-stimulation in rats.

Pimozide is a potent antagonist to amphetamine- and apomorphine-induced stereotype in most animal species tested. It also blocks apomorphine-induced emesis.

Pimozide has little activity in the norepinephrine test in rats.

Typical neuroleptic catalepsy was observed in 8 out of 8 monkeys treated with 0.8 mg/kg pimozide. Obvious to severe extrapyramidal (dystonic) effects were observed at the same doses in 4 out of 8 pimozide-treated monkeys.

Pimozide causes no significant alterations in the hemodynamic parameters in cardiovascular experiments in rats, dogs, and dwarf pigs. It is a weak hypotensive agent and norepinephrine antagonist in rats and dogs, and exhibits very weak alpha-adrenergic blocking activity in dogs. In other tests, it has been found to antagonize the action of angiotensin on rat colon and rabbit aorta.

Bio- and histochemical-studies in rats have indicated that, at the lower-dose levels, pimozide is a highly selective blocker of central dopamine receptors and increases turnover of dopamine in the central nervous system. At higher doses, increased turnover of noradrenaline has also been observed.

The following table shows dosage details for some of the above-mentioned tests:

Activity Profile of Pimozide

	PIM mg/kg	
Pharmacological Test	**S.C.**	**P.O.**
Lowest dose producing at least 40% ptosis	2.5	2.5
Catalepsy: ED_{50}	0.2	0.22
Ptosis/Catalepsy ratio	12.5	11.0
Jumping box: ED50	0.11	0.09
Sidman shock avoidance: 50% inhibition	0.16	---
Noise escape: ED50	0.17	---
Intracranial self-stimulation: **- 50% decrease** **- 90% increase**	 0.2 0.6	 --- ---
Anti-apomorphine test: lowest ED50 **	0.17	---
Anti-amphetamine test: lowest ED50 **	0.11	---
Anti-norepinephrine test: lowest ED50 **	- 40	---
Anti-apomorphine test (dogs): lowest ED50	0.012	0.018
Jumping box (dogs): ED50	0.1	0.2

* Results from earlier pharmacological studies.
**The ED_{50}'s varied with time after administration; on the anti-apomorphine test, the lower ED_{50} with PIM occurred at 4 hours, the peak value on the anti-amphetamine test occurred at 4 hours and at 2 hours on the anti-norepinephrine test.

Metabolism: Pimozide is well absorbed after oral administration, as demonstrated by the similarity of effective oral and parenteral doses. In rats, approximately 10% of the radioactivity of tritium-labelled doses is stored in the liver, 0.7% in blood, and 0.1% in the brain throughout the first 8 hours; thereafter the concentration in the brain decreases more slowly than that in blood and the liver. Detectable levels of radioactivity have been found in all three tissues 64 hours after the injection. In the brain, the concentration of radioactivity is highest in the caudate nucleus. Peak levels of unchanged pimozide occur one hour after injection, whereafter they gradually decrease at a similar rate in all three tissues. The biological half-life of pimozide in rats has been estimated to be 5.6 hours. At one hour the percentage unchanged pimozide of total tritiated material was 84% in the brain, 47% in blood and 33% in the liver. The liver contained approximately 36 times more unchanged pimozide than the brain and about 11 times more than blood. When tritium-labelled pimozide was given subcutaneously to dogs, 0.13% of the dose was recovered in the brain 6 hours following the injection. Virtually all of the radioactivity present was due to unchanged pimozide. The highest concentrations were found in the pituitary gland and the caudate nucleus.

The major metabolic pathway in rats is oxydative N-dealkylation, the main metabolites being 4-bis (p-fluorophenyl) butyric acid and N-4-piperidyl-2-benzimidazolinone. It is thought that the metabolites are pharmacologically inactive, since peak pharmacological activity has been found to correlate with maximum brain levels of unchanged pimozide, but not of the total radioactivity. Most of the injected pimozide is excreted within 48 hours in rats. When ^{14}C-labelled drug was used, 32% of the radioactivity was excreted in urine, mainly as N-4-piperidyl-2-benzimidazolinone, and 42% in the feces, half as unchanged pimozide, half as N-4-piperidyl-2-benzimidazolinone. With ^{3}H-labelled pimozide, excretion was mainly in the feces as unchanged pimozide and as 4-bis (p-fluorophenyl) butyric acid and bis (p-fluorophenyl) acetic acid.

TOXICOLOGY

Acute Toxicity

The following table presents the results of the acute pimozide toxicity studies in rats, mice, hamsters and dogs.

Species	Sex	Route & Vehicle*	LD50 mg/kg (95% confidence limits)**
Rat	M	Oral(1)	> 5120
	F	Oral(2)	1430 (996-2116)
	M	S.C.(4)	> 40
	M	I.V.(4)	> 5
Mouse	M	Oral(1)	228 (141-369)
	M&F	Oral(2)	> 640
	M	S.C.(4)	> 40
	M	I.V.(4)	11.1 (7.4-16.7)
Hamster	M	Oral(2)	1100 (524-2310)
	F	Oral(2)	550 (249-1216)
Dog	M&F	Oral(3)	~ 40
	M&F	Oral(2)	> 80
	M&F	S.C.(4)	> 5

* 1. UItrasonically micronized aqueous suspension.
2. Suspension in Tween 80+ Syrup.
3. Capsules.
4. Aqueous solution with 0.1 M tartaric acid.

** Due to the poor solubility of pimozide in an aqueous medium, few actual LD_{50}'s could be determined; the results varied widely with the vehicle in which the drug was administered.

When death occurred: it was frequently delayed for several days.

The main toxic symptoms noted in all species were sedation, catalepsy, and prelethal clonic seizures. In dogs, doses as low as 0.16 mg/kg *p.o.* or *i.v.* induced catalepsy and sedation, while ataxia and clonic seizures were observed at 20 mg/kg or more orally.

Subacute Toxicity

In a 14-week study, pimozide was administered in the diet in doses of 0, 0.04, 0.31 and 2.5 mg/kg/day. Sedation, decreased food consumption and reduced body weight gain were noted in the 2.5 mg/kg group only. At this dosage level, there was also a significant decrease in the absolute organ weights for almost all organs and an increase in the relative weight of the brain. No significant gross or histopathological changes were observed.

Eight dogs were given pimozide orally in gradually increasing doses from 4 to 24 mg/kg/day. Six of the animals completed 4 to 5 weeks on the drug, one male dog died on day 15 after a week on 16 mg/kg/day (ataxia and daily convulsions), and another male was removed from the study on day 16 after a week on 24 mg/kg/day, following convulsions, emesis, anorexia and a very depressed state. All animals exhibited hyperactivity, convulsions, decreased food intake, emesis and weight loss. Some hemorrhages were observed on gross pathological examination, but there were no drug-related histopathological abnormalities.

Chronic Toxicity

In an 18-month study, rats received 0, 0.025, 0.21, 1.7 and 13.3 mg/kg/day pimozide in the diet. Health, behaviour and appearance were normal in the low- and medium-dose rats throughout the study. In the two high-dose groups, sedation was noted in the first week and persisted throughout the study in the highest dose group. Decreased food consumption and body weight gain occurred also from the first week of dosing in the two high-dose groups and persisted throughout the experiment.

The only pathological change clearly related to pimozide administration was mammary activation in most medium- and high-dose females and 2 high-dose males. This response is a common feature of all potent neuroleptics, and it was observed as early as 6 months after initiation of drug administration. Gonadal atrophy was noted terminally in a number of the males and some females. Necropsy at 18 months showed a decreased absolute weight of most organs of the animals in the two high-dose groups, while the relative weight of the brain in these groups was increased compared with controls. Significant histopathological changes were noted only in the two higher dosage groups. In the spleen there was a tendency to more hemosiderin and an increased number of lipofuscin-loaded macrophages and plasmocytes. The mesenteric lymph nodes also showed a tendency to an increased number of histiocytes in the sinuses and lipofuscin-loaded macrophages. The adrenals had minimal changes in the cortex, such as a slightly more fatty fasciculata and a few more lipofuscin-loaded cells in the reticularis in the 13.3 mg/kg dose animals. Females in both higher dosage groups had atrophic uteri and more mucified vaginas, while males had some mammary ductular development, as well as depressed secretory activity, inflammation and fibrosis of the prostate gland. Hypophyseal alterations consisted of increased numbers and signs of chronic stimulation of the erythrosinophils in both male and female rats and decreased numbers and signs of depression of the basophils in male animals. There was a greater tendency to fatty bone marrow in the highest dose animals.

In a one-year study, 40 Beagle dogs received pimozide orally 7 days a week at dose levels of 0, 0.5, 1.5 and 3 mg/kg/day. No deaths occurred at these dosages. In the treated groups, effects attributed to drug administration were mild sedation, muscular tremors, and mammary and gingival hyperplasia. Body weight loss was observed in the 3 mg/kg group only. Sedation and tremors occurred at first in most dogs, gradually decreasing in frequency and becoming rare or absent during the last nine months. Mammary hyperplasia occurred in females only and had completely regressed in all animals by the third month of the study. Lactation was observed in one high and one medium-dose female. During the seventh month, gingival hyperplasia appeared in all high- and medium-dose dogs. The severity of the gingival hyperplasia was dose-related and the lesions persisted in all but one dog to the end of the study. There were no significant drug effects on hematology, coagulation, clinical chemistry, urinalysis, and ophthalmology. S-T and T-wave changes occurred more frequently in treated than control animals. Two animals from each group were kept for observation for 20 weeks following the termination of the one-year study. Drug withdrawal had no apparent effect on the usual clinical parameters in these dogs. However, histopathological evaluation revealed gingival hyperplasia in all mid- and high-dose animals, although only one high-dose dog showed signs of regressed gingival hyperplasia macroscopically. Evidence of mammary hyperplasia was also observed in the mid- and high-dose females.

Carcinogenicity Studies

Mice were given pimozide as a drug/diet mixture at dosage levels of 0, 0.62, 5.0 and 40.0 mg/kg/day for 18 months. A dose-related sedative effect was noted at the 5 and 40 mg/kg dose levels.

Carcinogenicity studies revealed no treatment related tumors in rats or male mice, but increased incidences of pituitary adenomas and mammary gland adenocarcinomas in female mice.

These histopathology changes in the mammary gland and pituitary are thought to be prolactinmediated and have been shown in rodents following hyperprolactinemia by a variety of neuroleptic drugs with the relevance to humans being questionable.

In a 24-month carcinogenicity study in rats, pimozide was mixed with the animals' normal daily diet at dosage levels of 0, 0.31, 2.5 and 20 mg/kg/day.

Clinical observations included paraphimosis in high-dose males and emaciation in mid- dose females and high-dose animals of both sexes. In addition, the testes of male rats in all drug groups were undersized and/or soft.

Reproductive Studies

In two studies, pimozide was administered to female Wistar rats for the first 21 days of pregnancy: 0.16, 0.63, 2.5 and 10 mg/kg/day subcutaneously in one study and 0.04, 0.31 and 2.5 mg/kg/day by gavage in the other study. At 2.5 and 10 mg/kg *s.c.* and 2.5 mg/kg *p.o.* the food intake and weight gain of dams were decreased and their mortality rates increased. The number of pregnancies in these high-dose groups was also decreased. In the 10 mg/kg s.c. group there were no live births, all fetuses being resorbed, while in the 2.5 mg/kg *s.c.* group the average litter size and % live fetuses were decreased and % resorptions increased. The average birth weight of pups in both 2.5 mg/kg groups was significantly lower than in the control group, and in the orally treated group most pups showed retarded, although normal, embryological development. With the exception of the 0.63 mg/kg dams, which showed increased resorptions and lower birth weight of pups, no adverse effects were noted in the other treated groups. Pimozide, at doses of 0.04, 0.31 and 2.5 mg/kg/day, was also administered in the diet to male rats for 60 days pre-mating and to female rats for 14 days pre-mating throughout pregnancy. No effect was noted on male or female fertility, but the estrus cycle of dosed females was increased. No abnormalities were observed among the offspring, although the percentage of stillborn was slightly increased in the high-dose group. In a fourth rat study, 0, 0.4, 0.31 and 2.5 mg/kg/day was administered in the diet to pregnant females through days 6 to 15 of pregnancy. No significant effects were noted in any of the treated groups, although in the high-dose group the average food intake of dams was lower, the % resorptions slightly increased, and the average litter size and birth weight of pups was slightly smaller. Finally, pimozide 0, 0.04, 0.31 and 2.5 mg/kg/day was given to female rats in the diet during the last third of pregnancy and lactation. There was a decrease in the weight gain of the 2.5 mg/kg dams during the last week of pregnancy. Compared with controls, the average litter size in this group was slightly smaller, the average birth weights slightly lower, and the % of stillborn pups considerably higher. The survival rate of pups at weaning was reduced in all the treated groups in a dose-related manner.

Two studies were conducted in rabbits, pimozide being administered during days 6 to 18 of pregnancy in both. In the first study, 0, 0.16, 0.31, 0.63, 1.25 and 2.5 mg/kg/day was given by gavage to Belgian hares. There was a dose-related decrease in the percent of females found pregnant at the end of the study. No other effects were observed apart from a decrease in litter size in the 1.25 mg/kg group and a slight decrease in the birth weights in the 0.63, 1.25 and 2.5 mg/kg groups. In the second study, New Zealand white rabbits received 0, 0.16, 0.63 and 2.5 mg/kg/day pimozide, also by gavage. In the high-dose group, mortality was increased and the number of pregnancies slightly reduced. A dose-related decrease in the body weight gain was

noted in all treated groups. A dose-related decrease in the average litter size was also seen in all treated groups. In the 2.5 mg/kg group, the % resorptions was increased and the % live fetuses decreased, but no other abnormalities were observed.

Mutagenicity

The results of mutagenic studies indicate no genotoxicity.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse-dominant lethal test or in the micronucleus test in rats.

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PART III: CONSUMER INFORMATION

PrPIMOZIDE
Pimozide Tablets USP

This leaflet is part III of a three-part "Product Monograph" published when PIMOZIDE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PIMOZIDE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Pimozide is used to control the symptoms of chronic schizophrenia where the main manifestations do not include excitement, agitation or hyperactivity.

What it does:
Pimozide is an antipsychotic medication which affects chemicals in the brain that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. Exactly how Pimozide works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

When it should not be used:
Pimozide should not be used to manage mania or acute schizophrenia.

You should not use Pimozide if you:
- Have an allergy to pimozide, to any of the ingredients in Pimozide or components of the container, or to phenothiazines
- Have a medical condition known as pheochromocytoma (a tumor of the adrenal gland)
- Have a severe heart disorder or a family history of heart disorders such as long QT syndrome, Torsade de Pointes or arrhythmia
- Have a severe blood vessel or blood disorder
- Have severe kidney problems
- Have had brain damage
- Have liver disease
- Have a blood cell disorder such as anemia, low white blood cell counts, low platelets
- Have drowsiness, slow breathing, weak pulse
- Have decreased alertness caused by taking certain medications or drinking alcohol
- Are going to receive anesthesia in the spine or for a region (such as an arm, leg or the lower part of your body)
- Have Parkinson's syndrome
- Have a depressive disorder
- You are under treatment of tics
- You have family history of irregular heartbeats.
- Have central nervous system depression or comatose states
- Are being treated with the following drugs:
  I. CYP 3A4-inhibiting drugs such as antifungal drugs (e.g.micronazole, ketonazole), antiviral (e.g. Saquinavir, Ritonavir), macrolide antibiotics (e.g. Clarithromycin and erythromycin) and nefazodone.
  II. CYP 2D6-inhibiting drugs such as quinidine
  III. Selective Serotonin Reuptake Inhibitor antidepressants such as sertraline, paroxetine, citalopram and escitalopram.

What the medicinal ingredient is:
Pimozide.

What the nonmedicinal ingredients are:
Anhydrous Lactose, Croscarmellose Sodium, Magnesium Stearate.

4 mg Tablets: contains additional D & C Yellow #10 Aluminium Lake 14-18%, Indigotine AL Lake 12-14% (Blue #2).

What dosage forms it comes in:
Tablets, 2 mg and 4 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Studies with various medicines of the group to which pimozide belongs, when used in the elderly patients with dementia, have been associated with an increased rate of death. Pimozide is not indicated in elderly patients with dementia.

BEFORE you use Pimozide talk to your doctor or pharmacist if:
- You have a history of problems with the heart and/or blood vessels
- You are prone to low blood pressure (hypotension)
- You have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reason, or take oral contraceptives ("The Pill")
- You have glaucoma or prostatic hypertrophy
- You are addicted to alcohol. You should not take Pimozide if you are under the effects of alcohol
- You are pregnant. Pimozide should not be used during pregnancy unless your doctor considers the benefits to you markedly outweigh the potential risks to the fetus
- You are taking barbiturates, painkillers, narcotics or, antihistamines or other drugs that make you drowsy
- You have any allergies to this drug or its ingredients
- You have or ever had a blackout or seizure
- You are breast feeding

- You have a history of breast cancer

Pimozide may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. You should be cautious when performing potentially hazardous tasks.

Effects on Newborns:
In some cases, babies born to a mother taking Pimozide during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your newborn if they have difficulty breathing, are overly sleepy, have muscle stiffness, or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

People who take Pimozide are cautioned:
- Against exposure to extreme heat
- That drugs such as Pimozide increase the toxicity of certain types of insecticides ("organophosphorous" insecticides) including insecticides for agriculture (farming), treating animals (flea and tick control) and for treating pests around the house and garden. Be cautious if you must use these products while taking Pimozide.

INTERACTIONS WITH THIS MEDICATION

Pimozide can add to the effects of alcohol. You should avoid consuming alcoholic beverages while on Pimozide therapy.

Because substances in grapefruit juice may interact with Pimozide, you should avoid grapefruit juice when taking Pimozide.

Tell your doctor about all your prescription and over-the-counter medications, vitamins, minerals, herbal products (such as St. John's Wort), and drugs prescribed by other doctors. Do not start a new medication without telling your doctor.

Before using Pimozide, tell your doctor if you regularly use other medicines that make you sleepy (such as cold or allergy medicine, narcotic pain medicine, sleeping pills, muscle relaxants, and medicine for seizures, depression, or anxiety). You should not take Pimozide if you have drowsiness caused by other medications.

Some MEDICINES MAY INTERACT with Pimozide. Tell your health care provider if you are taking:
Anti-anxiety agents, antidepressants, muscle relaxants, antiseizure medicine, high blood pressure medicine, cabergoline, metrizamide, guanethidine, guanadrel, grepafloxacin, sparfloxacin, lithium, cisapride, atropine-like drugs, narcotic pain relievers (e.g., codeine), drugs used to aid sleep, drowsiness-causing antihistamines (e.g., diphenhydramine), other drugs that may make you drowsy, levodopa, antimicrobial and antiviral medications (such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and analogues, quinolone antibiotics, pentamidine, antimalarials (i.e. quinine), amphotericin B), antiarrhythmics, antipsychotics, domperidone, 5-HT3 antagonists, tacrolimus, beta-2-adrenoceptor agonists, diuretics, laxatives and enemas and high dose corticosteroids.

Many cough-and-cold products contain ingredients that may add a drowsiness effect. Before using cough-and-cold medications, ask your doctor or pharmacist about the safe use of those products. Do not start or stop any medicine without doctor or pharmacist approval.

This list is not complete and there may be other drugs that can interact with Pimozide.

PROPER USE OF THIS MEDICATION

Take this medication by mouth exactly as prescribed. During the first few days your doctor may gradually increase your dose to allow your body to adjust to the medication. Do not take this medication more often or increase your dose without consulting your doctor. Your condition will not improve any faster but the risk of serious side effects will be increased. Do not stop taking this drug suddenly without your doctor's approval.

Your doctor will decide which dose is best for you.

Adult usual dose:
Pimozide is usually taken once daily in the morning. Follow your doctor's instructions.

Take Pimozide tablets with a full glass of water.

Pimozide is not recommended for use in patients under 18 years of age or in patients 65 years of age or older.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Overdose symptoms may include irregular heartbeat, low blood pressure, agitation, and confusion, drowsiness, dizziness, muscle stiffness or twitching, increased salivation, trouble swallowing, weakness, loss of balance or coordination, and fainting

Missed Dose:
Take the missed dose as soon as you remember. If it is almost time for the next dose wait until then to take the medicine and skip the missed dose. Do not double your dose to make up the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like other medications, Pimozide may cause some side effects. These side effects may be minor and temporary. However, some may be serious and need medical attention.

Side effects may include: sweating, urinary incontinence, severe constipation, dizziness, drowsiness, dry mouth, nasal congestion, nausea and vomiting, headache, menstrual changes, change in libido, swelling of the breasts and milk production in both men and women, weight changes and blurred vision.

If any of these affects you severely, tell your doctor.

Your doctor should check your body weight before starting Pimozide and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting Pimozide to monitor blood sugar, and the number of infection fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism you may be at increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Side Effect / Symptom		Talk with your Doctor or Pharmacist		Stop taking drug and seek immediate emergency assistance
		Only if severe	In all cases	
Unknown	**Allergic Reaction**: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Neuroleptic Malignant Syndrome: any group of symptoms which may include high fever, sweating, stiff muscles, fast heartbeat, fast breathing and feeling confused, drowsy or agitated			✓
	Extrapyramidal Symptoms: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want			✓
	Fast or irregular heartbeat		✓	
	Seizures or fits			✓
	Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations		✓	
	Long-lasting (greater than 4 hours in duration) and painful erection of penis			✓
	Tardive Dyskinesia: uncontrollable movements or twitches of the body, face, eyes or tongue, stretching the neck and body		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Side Effect / Symptom		Talk with your Doctor or Pharmacist		Stop taking drug and seek immediate emergency assistance
		Only if severe	In all cases	
	Low Blood Pressure: feeling of lightheadedness or fainting especially when getting up from a lying or sitting position		✓	
	High Blood Pressure: headaches, vision disorders, nausea and vomiting		✓	
	Decreased sweating		✓	
	Jaundice: yellow color to skin and eyes, dark urine		✓	
	Respiratory Infection: fever, flu-like symptoms, coughing, difficult or fast breathing		✓	
	New or worsening Constipation		✓	
	Akathisia: a feeling of restlessness, inability to remain motionless		✓	
	Vision Changes: blurred vision, glaucoma or other eye disorder		✓	
	Increased Blood Sugar: frequent urination, thirst and hunger	✓		

This is not a complete list of side effects. For any unexpected effects while taking PIMOZIDE, contact your doctor or pharmacist.

HOW TO STORE IT

Store Pimozide tablets at room temperature (15°C-30°C) in well-closed containers.

Do not use after the expiry date shown on the bottle.

Keep this medication and all medications out of the reach and sight

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, AA Pharma Inc. at:

1-877-998-9097

This leaflet was prepared by AA Pharma Inc., Vaughan, Ontario, L4K 4N7.

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