

Aldazine

Thioridazine hydrochloride

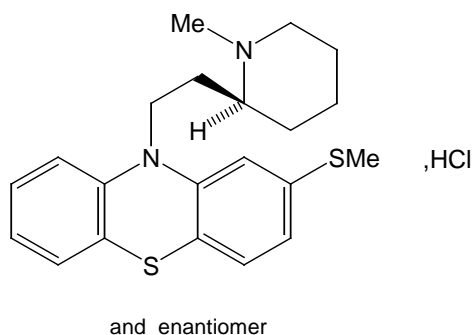


PRODUCT INFORMATION

Name of the Medicine

The active ingredient of Aldazine tablets is thioridazine hydrochloride.

The chemical name for thioridazine hydrochloride is (RS)-10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio)-phenothiazine hydrochloride. Its structural formula is:



Molecular formula: $C_{21}H_{26}N_2S_2, HCl$

Molecular weight: 407.0

CAS Registry No.: 130-61-0

Description

Thioridazine hydrochloride is a white or almost white, crystalline powder. It is freely soluble in water and in methanol, soluble in alcohol, practically insoluble in ether.

Each Aldazine 10 tablet (bottle - AUST R 17568) contains 10 mg of thioridazine hydrochloride and the following inactive excipients: lactose, cellulose - microcrystalline, starch - pregelatinised maize, dextrates, sodium starch glycollate, silica - colloidal anhydrous, talc - purified, magnesium stearate, hypromellose, diethyl phthalate, Opadry Green OY-S-8836 and carnauba wax. *The tablets are gluten free.*

Each Aldazine 10 tablet (blister pack - AUST R 93654) contains 10 mg of thioridazine hydrochloride and the following inactive excipients: lactose, cellulose - microcrystalline, starch - pregelatinised maize, dextrates, sodium starch glycollate, silica - colloidal anhydrous, talc - purified, magnesium stearate and Opadry II Green OY-LS-21010. *The tablets are gluten free.*

Each Aldazine 25 tablet (bottle - AUST R 53177, blister pack - AUST R 53178) contains 25 mg of thioridazine hydrochloride and the following inactive excipients: cellulose - microcrystalline, starch - pregelatinised maize, dextrates, sodium starch glycollate, silica - colloidal anhydrous, talc - purified, magnesium stearate hypromellose, diethyl phthalate and Opadry Brown OY-S-9455. *The tablets are gluten free.*

Each Aldazine 50 tablet (bottle - AUST R 17571, blister pack - AUST R 17597) contains 50 mg of thioridazine hydrochloride and the following inactive excipients: cellulose - microcrystalline, starch - pregelatinised maize, dextrates, sodium starch glycollate, silica - colloidal anhydrous, talc - purified, magnesium stearate, hypromellose, diethyl phthalate, Opadry Green OY-S-8844 and carnauba wax. *The tablets are gluten free.*

Each Aldazine 100 tablet (bottle - AUST R 49813, blister pack - AUST R 49814) contains 100 mg of thioridazine hydrochloride and the following inactive excipients: lactose, cellulose - microcrystalline, starch - pregelatinised maize, dextrans, sodium starch glycolate, silica - colloidal anhydrous, talc - purified, magnesium stearate, hypromellose, diethyl phthalate and Opadry Green OY-C-8819. *The tablets are gluten free.*

Pharmacology

Pharmacodynamics

Aldazine is a piperidine phenothiazine derivative with a psychosedative action and in low doses it is an anxiolytic agent. In high doses Aldazine is a neuroleptic with minimal antiemetic activity and minimal extrapyramidal effects, notably parkinsonism. The presence of a thiomethyl radical (S-CH₃) in position 2, conventionally occupied by a halogen, is unique and could account for the relatively low extrapyramidal effect, minimal antiemetic action, and moderate sedative effect of thioridazine compared with other phenothiazines.

Pharmacokinetics

Absorption. Thioridazine is readily absorbed from the gastrointestinal tract and widely distributed throughout the body. It readily diffuses across the placenta. Plasma concentrations from a given dose show wide inter-individual variation and are higher in the elderly. The average systemic bioavailability is approximately 60% and maximum plasma concentration is reached two to four hours after administration.

Distribution. The apparent volume of distribution is approximately 3.5 L/kg with protein binding above 95%. Thioridazine crosses the placenta and passes into breast milk.

Metabolism and excretion. Thioridazine is metabolised in the liver and excretion is via the faeces (50%) and the urine (more than 30%). Less than 4% of the dose is excreted unchanged in the urine. Plasma elimination half-life is approximately 10 hours. Some of the metabolites (e.g. mesoridazine, sulforidazine) possess pharmacodynamic properties similar to those of the parent compound.

Indications

Management of adult schizophrenic patients who have failed to respond adequately to treatment with appropriate courses of at least two other antipsychotic drugs, at an adequate dose and for an adequate duration, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs (see Contraindications and Precautions).

Contraindications

- Hypersensitivity to thioridazine base, thioridazine hydrochloride or to any of the excipients in the formulations.
- Comatose states or severe depression of the central nervous system from any cause including drug induced central nervous system depression (see Precautions).
- In combination with other drugs that are known to prolong the QTc interval and in patients with congenital long QT syndrome or a history of cardiac arrhythmias.
- Severe cardiovascular disease, especially clinically relevant arrhythmias, e.g. torsades de pointes.
- In combination with other drugs that inhibit cytochrome P450 2D6 isozyme activity or otherwise appreciably inhibit the metabolism of thioridazine, as well as in patients who are known to have a genetic defect leading to reduced levels of cytochrome P450 2D6 activity (see Interactions).

- Bone marrow depression.
- History of blood dyscrasia or hypersensitivity to other phenothiazines (such as severe photosensitivity or other hypersensitivity reactions).
- In combination with other neuroleptic agents.
- Pick's disease.
- Children.

Precautions

Potential for Proarrhythmic Effects

Due to the potential for significant, possibly life-threatening, proarrhythmic effects with thioridazine treatment, Aldazine should be reserved for use in the treatment of adult schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Consequently, before initiating treatment with Aldazine, it is strongly recommended that a patient be given at least two trials, each with a different antipsychotic drug product, at an adequate dose, and for an adequate duration. Thioridazine has not been systematically evaluated in controlled trials in the treatment of refractory schizophrenic patients and its efficacy in such patients is unknown.

A crossover study in nine healthy males comparing single doses of thioridazine 10 mg and 50 mg with placebo demonstrated a dose-related prolongation of the QTc interval. The mean maximum increase in QTc interval following the 50 mg dose was about 23 msec; greater prolongation may be observed in the clinical treatment of unscreened patients.

Thioridazine has been shown to prolong the QTc interval in a dose related manner. Prolongation of the QTc interval has been associated with the ability to cause torsades de pointes-type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death. There are several published case reports of torsades de pointes and sudden death associated with thioridazine treatment. A causal relationship between these events and Aldazine therapy has not been established but, given the ability of thioridazine to prolong the QTc interval, such a relationship is possible.

The following circumstances may increase the risk of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval: bradycardia, hypokalaemia, underlying cardiovascular disease, a history of arrhythmias while taking phenothiazines, concomitant use of other drugs that prolong the QTc interval, presence of congenital prolongation of the QT interval, and for thioridazine in particular, its use in patients with reduced activity of P450 2D6 or its co-administration with drugs that may inhibit P450 2D6 or by some other mechanism interfere with the clearance of thioridazine (see Contraindications and Precautions).

It is recommended that a baseline ECG be performed and serum potassium and magnesium levels measured in patients being considered for thioridazine treatment. Serum potassium and magnesium should both be normalised before initiating treatment and patients with a QTc interval greater than 450 msec should not receive thioridazine treatment. During treatment, it may be useful to periodically monitor ECG's and serum potassium and magnesium, especially during a period of dose adjustment. In addition, the lowest effective dose of thioridazine should be used. Patients who are found to have a QTc interval over 500 msec should discontinue thioridazine treatment.

Further cardiac evaluation may be warranted in patients who experience symptoms that may be associated with the occurrence of torsades de pointes (e.g. dizziness, palpitations or syncope). In particular, Holter monitoring should be considered.

Patients should be informed that thioridazine has been associated with potentially fatal heart rhythm disturbances. The risk of such events may be increased when certain drugs are given together with thioridazine. Therefore, patients should inform the prescriber that they are receiving Aldazine treatment before taking any new medication.

Effects on Ability to Drive and Use Machinery. Patients receiving thioridazine should be cautioned that impairment of reaction, blurred vision, drowsiness and other CNS symptoms may occur (see Adverse Reactions), in which case they should not participate in activities requiring complete mental alertness, for example, driving motor vehicles or operating machinery. Patients should also be warned that alcohol or other drugs may potentiate these effects (see Interactions).

Blood Dyscrasias. Anxiolytic doses of thioridazine very rarely cause leucopenia. With neuroleptic doses, leucopenia and agranulocytosis have been reported occasionally, so regular blood counts should be carried out during the first 3 to 4 months of treatment and immediately on the appearance of suspicious clinical signs.

Possible Thromboembolic Complications. As with other neuroleptics, an increased risk of thromboembolic complications has been observed, possibly as a result of immobilisation. Care should, therefore, be taken to ensure that patients do not become bedridden. In the event that a patient becomes bedridden, prophylactic measures against thrombosis are recommended.

Thermoregulatory Effects. Aldazine may affect the temperature regulatory centre. In addition, its anticholinergic properties may prevent sweating during heatwaves; therefore patients should not be exposed to extreme conditions. This applies especially when high doses are being taken or when concurrent antiparkinson medication is being given.

Anticholinergic Effects. Because of its anticholinergic effects, thioridazine should be used with caution in patients with a history of increased intraocular pressure, narrow angle glaucoma, urinary retention (e.g. due to prostatic hypertrophy) and chronic constipation. On account of its anticholinergic properties, thioridazine should be used with caution in patients with myasthenia gravis and dementia (see Contraindications).

Cardiovascular Effects. Caution is advised in patients with a history of cardiovascular disease, especially in the elderly and in those with congestive heart failure, conduction disorders, arrhythmias, or circulatory lability (see Contraindications). Risk factors for the development of cardiac arrhythmias include underlying cardiovascular disease (severe cardiovascular diseases are a contraindication), hypokalaemia and a history of arrhythmias while taking phenothiazines.

Hypotension. Orthostatic hypotension is commonly observed in patients taking thioridazine (see Dosage and Administration – Monitoring Advice). When starting treatment with thioridazine it is advisable to check blood pressure, especially in the elderly and in patients with postural hypotension or a labile circulation. Female patients appear to have a greater tendency to orthostatic hypotension than male patients. If treatment of drug-induced hypotension is required, the potent α -adrenergic blocking properties of the phenothiazines make the use of vasopressors with mixed α - and β -adrenergic agonist properties, including adrenaline and dopamine, inappropriate. Blockade of α -receptors may lead to unopposed β -adrenergic activity, causing β -adrenergic-mediated vasodilation and severe hypotension.

Seizures. Thioridazine can lower the seizure threshold and induce discharge patterns in the EEG that are associated with epileptic seizure disorders. In cases where thioridazine is used in epileptic patients, anticonvulsant medication should be maintained, antipsychotic dosage increased gradually, and the possibility of interactions considered. Dosage adjustments of anticonvulsant medications may be necessary (see Interactions).

Ocular Effects. Pigmentary retinopathy has been reported after long-term treatment, mostly in patients who received doses exceeding the recommended maximum of 800 mg/day. The disorder is characterised by diminution of visual acuity, brownish colouring of vision and impairment of night vision. Examination of the fundus discloses deposits of pigments. (See Dosage and Administration – Monitoring Advice.)

Extrapyramidal Effects. A variety of neurological syndromes, in particular involving the extrapyramidal system, occur following the use of many antipsychotic drugs: acute dystonia, akathisia, parkinsonism, and tardive dyskinesia. Extrapyramidal symptoms may occur, especially with high (neuroleptic) doses of thioridazine (see Adverse Reactions). For this reason great care should be taken if thioridazine has to be used in a patient with Parkinson's disease.

Tardive dyskinesia. A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients on antipsychotic drugs. The disorder consists of repetitive involuntary movements of the tongue, face, mouth or jaw (e.g. protrusion of the tongue, puffing of the cheeks, puckering of the mouth, chewing movements). The trunk and limbs are less frequently involved. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of the drug increases. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses. The risk seems to be greater in elderly patients, especially females.

The syndrome may become clinically recognisable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Neuroleptic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby possibly mask the underlying disease.

Given these conditions, Aldazine should be prescribed in a manner that is most likely to minimise the occurrence of tardive dyskinesia. In patients who require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be assessed periodically.

It is generally believed that reversibility is more likely after short-term rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of thioridazine should be reduced periodically (if possible) and the patient observed for signs of the disorder.

There is no known effective treatment for tardive dyskinesia. It is suggested that anti-psychotic agents be discontinued if symptoms of tardive dyskinesia appear. However, some patients may require neuroleptic treatment despite the presence of the syndrome. In that case, reduction to the minimum effective dose should be considered.

Effects on Prolactin. Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Although disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported (see Adverse Reactions), the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiological studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumourigenesis; the available evidence is considered too limited to be conclusive at this time.

Neuroleptic Malignant Syndrome. A potentially fatal syndrome called neuroleptic malignant syndrome (NMS) has been reported in association with anti-psychotic drugs, including thioridazine in very rare cases. The syndrome is characterised by muscular rigidity, fever, hyperthermia, altered consciousness and autonomic instability, irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnosis of NMS may be difficult. It must be differentiated from other conditions such as systemic infection, untreated or inadequately treated extrapyramidal symptoms, central anticholinergic toxicity, heat stroke, drug fever and primary CNS pathology.

In cases where NMS develops and in patients with unexplained high fever without additional clinical manifestations of NMS, thioridazine must be immediately discontinued and intensive monitoring and treatment of both the symptoms of NMS, and any associated medical problems are required.

For a patient requiring neuroleptic treatment after recovering from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS can occur.

Discontinuation of Therapy. Tolerance to the sedative effects of phenothiazines and cross tolerance among antipsychotic drugs have been reported. Tolerance may also underlie the clinical phenomenon of withdrawal-emergent dysfunctions. When long-term therapy is discontinued, a gradual reduction in dosage over several weeks is recommended, since abrupt withdrawal of neuroleptic drugs may cause some patients on high or long-term dosage to experience symptoms such as nausea, vomiting, gastric upset, trembling, dizziness, anxiety, agitation and insomnia as well as transient dyskinetic signs. These may falsely presage the onset of a depressive or psychotic episode.

Hepatic Impairment. In liver disease, regular monitoring of liver function is necessary.

Renal Impairment. The clearance of thioridazine can be decreased because of reduced renal function. Therefore, appropriate dosage adjustment may be required in patients with impaired renal function.

Lactose Warning. Because of the presence of lactose in Aldazine 10 mg and 100 mg tablets, these tablet strengths should not be used in patients with congenital galactosaemia, galactose malabsorption syndrome or lactase deficit.

Use in the Elderly

Elderly patients appear to be more prone to orthostatic hypotension and exhibit an increased sensitivity to the anticholinergic and sedative effects of phenothiazines. In addition, they are more susceptible to extrapyramidal side effects such as akathisia, tardive dyskinesia and parkinsonism. There appears to be an increased risk of agranulocytosis and leucopenia in the elderly. Careful observation during treatment and, if necessary, dosage adjustment are therefore advised.

Use in Children

See Contraindications.

Carcinogenicity/ Mutagenicity/ Impairment of Fertility

In embryotoxicity studies in rats and rabbits, thioridazine proved to be nonteratogenic. A 52 week toxicity study in rats and a six month toxicity study in dogs revealed no target organ toxicity. In a series of *in vitro* and *in vivo* tests, no mutagenic potential was detected for thioridazine.

Fertility and carcinogenicity studies have not been performed with thioridazine.

Use in Pregnancy (Category C)

During pregnancy thioridazine should only be prescribed under compelling circumstances. When given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the newborn infant.

Use in Lactation

Thioridazine passes into breast milk, possibly causing drowsiness and an increased risk of dystonia and tardive dyskinesia in the infant. Use of thioridazine during breastfeeding should therefore be avoided.

Interactions with other drugs

Patients should be informed that thioridazine has been associated with potentially fatal heart rhythm disturbances. The risk of such events may be increased when certain other drugs are given together with thioridazine.

Pharmacodynamic Interactions

CNS Depressants. Thioridazine may enhance the CNS depressant effects of analgesics, hypnotics, antihistamines, narcotics, alcohol, other CNS depressants such as benzodiazepines and general anaesthetics, and the antimuscarinic effects of anticholinergic agents, including atropine.

Anticholinergics. Concurrent use of anticholinergic agents with phenothiazines may exacerbate anticholinergic side effects, including atropine-like psychoses, severe constipation and adynamic ileus, and hyperpyretic effects potentially leading to heat stroke. Close supervision and dosage adjustment are therefore required when thioridazine is given concomitantly with drugs such as antihistamines, tricyclic antidepressants, atropine or atropine-like compounds.

Lithium. Concomitant use of lithium may aggravate extrapyramidal symptoms and neurotoxicity caused by neuroleptic agents. Severe neurotoxic complications, extrapyramidal side effects and sleep-walking episodes have been described in patients receiving lithium concurrently with phenothiazines, including thioridazine. Early signs of lithium toxicity may be masked by the antiemetic effect of thioridazine.

Alcohol. Since alcohol may potentiate the risk of hepatotoxic reactions, heat stroke, akathisia, dystonia or other disorders of the CNS, its consumption during thioridazine therapy should be avoided.

Monoamine Oxidase Inhibitors (MAOIs). Concurrent use with MAOIs may prolong and intensify the sedative and anticholinergic effects of either the MAOI or phenothiazines, including thioridazine.

Levodopa. The effects of both levodopa and thioridazine may be inhibited when these drugs are used concomitantly.

Adrenergic Vasoconstrictors. Owing to their adrenergic action, phenothiazines may reduce the pressor effect of adrenergic vasoconstrictors. Also, the use of adrenaline in the treatment of phenothiazine-induced hypotension may cause a reverse-adrenaline effect (see Precautions).

Drugs that Prolong the QTc Interval. There are no studies of the co-administration of thioridazine and other drugs that prolong the QTc interval. However, it is expected that such co-administration would produce additive prolongation of the QTc interval. Therefore, such use is contraindicated.

Quinidine. Phenothiazines may potentiate the inhibitory effect of quinidine on cardiac conduction.

Thiazide Diuretics. Concurrent use of phenothiazines and thiazide diuretics may result in severe hypotension, hyponatraemia and diuretic-induced hypokalaemia may potentiate thioridazine-induced cardiotoxicity.

Antidiabetic Agents. Phenothiazines affect carbohydrate metabolism and may, therefore, interfere with control of blood sugar in diabetic patients.

Ototoxic Medications. Concurrent use with phenothiazines may mask symptoms of ototoxicity such as tinnitus, dizziness or vertigo.

Pesticides. Phenothiazines may enhance the action of organophosphorous pesticides.

Pharmacokinetic Interactions

Thioridazine is metabolised by the cytochrome P450 2D6 isozyme and is itself an inhibitor of this pathway. The effects of thioridazine may therefore be increased and prolonged by drugs that inhibit this isozyme (e.g. fluoxetine, paroxetine, cimetidine and moclobemide), certain other drugs (e.g. fluvoxamine, propranolol and pindolol) and reduced activity of the isozyme itself. The resulting elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias such as torsades de pointes-type arrhythmias. Such an increased risk may also result from the additive effect of co-administering thioridazine with other agents that prolong the QTc interval. Thioridazine is, therefore, contraindicated with these drugs as well as in patients, comprising about 7% of the normal population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6 (see Precautions and Contraindications).

Drugs that Inhibit Cytochrome P450 2D6

In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25 mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to rapid hydroxylators. The rate of debrisoquin hydroxylation is thought to be dependant on the level of cytochrome P450 2D6 activity. Thus, this study suggests that drugs that inhibit P450 2D6 or reduced activity levels of this enzyme, will result in elevated levels of thioridazine. Therefore, the co-administration of drugs that inhibit P450 2D6 with thioridazine and the use of thioridazine in patients known to have reduced activity of P450 2D6 are contraindicated.

Drugs that Reduce the Clearance of Thioridazine through other Mechanisms

Fluvoxamine. The effect of fluvoxamine (25 mg twice daily for one week) on thioridazine steady state concentration was evaluated in 10 male in-patients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased three-fold following co-administration of fluvoxamine. Thioridazine and fluvoxamine should not be co-administered.

Propranolol. Increased plasma levels of thioridazine (approximately 50 to 400%) and its metabolites (80 to 300%) have been reported with concurrent administration of propranolol (100 to 800 mg daily). Thioridazine and propranolol should not be co-administered.

Pindolol. Concurrent administration with thioridazine have resulted in moderate, dose-related increases in the serum levels of thioridazine and its two metabolites, as well as higher than expected serum pindolol levels. Thioridazine and pindolol should not be co-administered.

Anticonvulsants. Phenothiazines, including thioridazine may lower the seizure threshold in epileptic patients. Serum levels of phenytoin may be raised or lowered by the use of thioridazine. Dosage adjustment of anticonvulsant medications may be necessary when taking thioridazine.

Tricyclic Antidepressants. As the combination of phenothiazines and tricyclic antidepressants may result in increased blood levels of both compounds, dose adjustment of one or both may be necessary. This is important as occasionally life-threatening arrhythmias have been reported in patients taking thioridazine and tricyclic antidepressants. These were usually at high or excessive dose of one or both medications. Also, the risk of neuroleptic malignant syndrome may be increased.

Barbiturates. Concomitant use of barbiturates with phenothiazines may result in reduced serum levels of both drugs and an increased response if one of the drugs is withdrawn.

Anticoagulants. Co-medication of anticoagulants with phenothiazines may cause an increased hypoprothrombinaemic effect, presumably due to enzyme competition, necessitating careful monitoring of plasma prothrombin.

Antacids and Antidiarrhoeal Drugs. These may inhibit the absorption of thioridazine. Antacids should not be used within two hours of taking thioridazine.

Beta-blockers. As a result of inhibition of metabolism, co-administration of beta-blockers with thioridazine may cause increased plasma concentrations of each medication, possibly resulting in severe hypotension, cardiac arrhythmias, irreversible retinopathy or CNS side effects.

Antihypertensives. Concurrent use with phenothiazines may produce severe hypotension with postural syncope.

Effects on laboratory tests

Urinary metabolites of phenothiazines may cause the urine to darken and result in false positive test results for urobilinogen, amylase, uroporphins, porphobilinogens and 5-hydroxyindolacetic acid. False positive test results for phenylketonuria may also occur during phenothiazine use. False positive or false negative pregnancy test results have reportedly occurred in some patients receiving phenothiazines. False positive antinuclear antibodies may also occur during phenothiazine use.

Adverse Reactions

Most side effects are mild and transient at the recommended doses. The adverse events included below have been reported with thioridazine.

Frequency estimate: Very common: $\geq 10\%$; common: $\geq 1\%$ to $< 10\%$, uncommon: $\geq 0.1\%$ to $< 1\%$; rare: $\geq 0.01\%$ to $< 0.1\%$; very rare: $< 0.01\%$.

Central nervous system

Very common. Sedation and drowsiness, especially where large doses are given early in treatment. Generally, this effect tends to subside with continued therapy or a reduction in dosage.

Common. Dizziness.

Uncommon. Confusion, agitation, hallucinations, irritability, headache.

Rare. Pseudoparkinsonism, convulsions, hyperkinesia, tardive dyskinesia, extrapyramidal symptoms (tremor, muscle rigidity, akathisia, dyskinesia, dystonia) with high doses of thioridazine. They are virtually unknown at the lower dose level.

Very rare. Depression, insomnia, nightmares, psychotic reactions, neuroleptic malignant syndrome.

Note. The doctor should look for early signs of tardive dyskinesia at regular intervals. For further details on extrapyramidal symptoms, tardive dyskinesia and neuroleptic malignant syndrome (see Precautions).

Autonomic nervous system

Common. Dry mouth, blurred vision, disturbances of accommodation, miosis, nasal congestion.

Rare. Pallor, tremor.

Cardiovascular system

Common. Orthostatic hypotension.

Uncommon. Tachycardia, ECG changes.

Rare. Arrhythmias.

Very rare. Peripheral oedema, torsades de pointes, sudden death (apparently due to arrhythmia or cardiac arrest).

Thioridazine produces a dose related prolongation of the QTc interval, which is associated with the ability to cause torsades de pointes type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death. Both torsades de pointes type arrhythmias and sudden death have been reported in association with thioridazine. A causal relationship between these events and Aldazine therapy has not been established but, given the ability of thioridazine to prolong the QTc interval, such a relationship is possible. Other ECG changes have been reported (see Precautions, Potential for Proarrhythmic Effects).

Endocrine system

Common. Galactorrhoea.

Uncommon. Amenorrhoea, menstrual irregularities, weight change, disturbances of erection (failure or priapism), inhibition of ejaculation.

Rare. Priapism.

Very rare. Breast engorgement.

Gastrointestinal system

Uncommon. Nausea, vomiting, diarrhoea, constipation, anorexia.

Very rare. Paralytic ileus.

Urinary system

Uncommon. Urinary retention or incontinence.

Blood

Rare. Leucopenia, agranulocytosis, thrombocytopenia.

Very rare. Anaemia, leukocytosis (see Precautions, Blood dyscrasias).

Liver

Uncommon. Abnormalities of liver enzymes.

Rare. Jaundice/hepatitis.

Skin

Rare. Dermatitis, skin eruptions, urticaria, allergic skin rashes, photosensitivity.

Other

Rare. Pigmentary retinopathy (see Precautions), hyperthermia, parotid swelling, respiratory depression.

Other Phenothiazine Derivatives

Efficacy, indications and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines (see Precautions). The most common neurological side effects in these patients are parkinsonism and akathisia. There appears to be an increased risk of agranulocytosis and leucopenia in the aged. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Central Nervous System. Akathisia, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Autonomic Nervous System. Constipation, anorexia, paralytic ileus.

Endocrine System. Altered libido, gynaecomastia, lactation, oedema. False positive pregnancy tests, decreased serum thyroxine concentrations, hyperglycaemia have been reported.

Skin. Erythema, exfoliative dermatitis, contact dermatitis.

Blood. Agranulocytosis, leucopenia, eosinophilia, thrombocytopenia, anaemia, aplastic anaemia, pancytopenia.

Allergic Reactions. Fever, laryngeal oedema, angioneurotic oedema, asthma.

Liver. Biliary stasis.

Cardiovascular. Changes in the terminal portion of the electrocardiogram, including prolongation of the QT interval, lowering and inversion of the T-wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving phenothiazines, including thioridazine. To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. However, significant prolongation of the QT interval has been associated with serious ventricular arrhythmias and sudden death (see Precautions). Hypotension, rarely resulting in cardiac arrest, has been reported.

Other. Systemic lupus erythematosus-like syndrome, progressive pigmentation of areas of skin, conjunctiva, sclera and cornea, irregular or stellate-shaped opacities of the anterior lens and cornea, hypercholesterolaemia.

Dosage and Administration

Since thioridazine is associated with a dose-related prolongation of the QTc interval, which is a potentially life-threatening event, its use should be reserved for schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Dosage must be individualised and the smallest effective dosage should be determined for each patient (see Indications and Precautions). The daily amounts of Aldazine are usually given in two to four divided doses.

Because the half-life of thioridazine is generally long, a full therapeutic effect may not be reached at a given dosage for several days until steady state plasma level is reached. In the case of schizophrenia, once effective control of symptoms has been achieved, the dosage may be reduced gradually to determine the minimum maintenance dose.

Adult Dosage	Usual starting dose	Daily dosage range
Ambulatory	100 mg three times daily	50 to 300 mg
Hospitalised	100 mg three times daily	100 to 600 mg

Considerably higher doses have been given, however, without any difficulties.

In underweight patients or those suffering from kidney or liver disease, as well as in elderly patients, lower initial doses and more gradual increases are indicated.

Maximum daily dose: 800 mg.

Monitoring Advice

Blood Pressure. When starting treatment with thioridazine it is advisable to check blood pressure, both recumbent and standing, especially in the elderly and patients with postural hypotension or a labile circulation (see Precautions – Hypotension). Whenever reviewing a patient on thioridazine, the blood pressure, both recumbent and standing, should always be checked, particularly during periods of dosage adjustment.

It is recommended that patients be considered for thioridazine treatment have a baseline ECG performed and both serum potassium and magnesium levels measured. It may also be useful to periodically monitor ECGs and both serum potassium and magnesium levels during thioridazine treatment, especially during a period of dosage adjustment (see Precautions – Potential for Proarrhythmic Effects).

Blood Counts. Regular blood counts should be performed during the first three to four months of treatment and also immediately on the appearance of suspicious clinical signs (see Precautions – Blood Dyscrasias).

Tardive Dyskinesia. To increase the likelihood of detecting tardive dyskinesia at the earliest possible time, the dosage of thioridazine should be reduced periodically (if possible) and the patient observed for signs of the disorder (see Precautions – Tardive Dyskinesia).

Eye Examinations. Periodic checks for ocular changes are recommended (see Precautions – Ocular Effects).

Liver and Renal Function. Regular monitoring is necessary in those with liver disease (see Precautions – Hepatic Impairment). Similarly, in patients with impaired renal function, regular monitoring of renal function is advisable (see Precautions – Renal Impairment).

ECG and serum potassium. Before initiating thioridazine therapy, a baseline ECG should be performed and serum potassium levels measured. During treatment, periodically monitor ECG's and serum potassium, especially during periods of dosage adjustment (see Precautions – Potential for Proarrhythmic Effects).

Overdosage

Many of the symptoms observed are extensions of those described under adverse reactions. Thioridazine can be toxic in overdose, with cardiac toxicity being of particular concern. Frequent ECG and vital sign monitoring of overdosed patients is recommended. Observation for several days may be required due to the risk of delayed effects.

Symptoms

Cardiovascular. Tachycardia, cardiac arrhythmia, severe hypotension, collapse, atrial fibrillation, ventricular flutter, torsades de pointes, AV-block or dissociation, Wenckebach heart block, bradycardia, cardiac arrest and death. Episodic ventricular tachycardia and fibrillation have been reported to occur 36 hours after overdosage with thioridazine.

Central Nervous System. Sedation, confusion, agitation, extrapyramidal effects, drowsiness, disorientation, hyperkinesia, convulsions, coma.

Autonomic Nervous System. Mydriasis, miosis, dry mouth, blurred vision, nasal congestion, urinary retention, hyperthermia.

Respiratory. Respiratory depression, respiratory arrest, pulmonary oedema.

Gastrointestinal. Paralytic ileus, nausea, vomiting.

Musculoskeletal. Rhabdomyolysis.

Treatment. There is no specific antidote for phenothiazine overdose. Treatment usually involves symptomatic support and careful monitoring of the cardiovascular, respiratory and central nervous systems.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Treatment may include one or more of the following interventions: correction of electrolyte abnormalities and acid-base balance, lidocaine, phenytoin, isoproterenol, ventricular pacing and defibrillation. Disopyramide, procainamide and quinidine may produce additive QT prolonging effects when administered to patients with acute overdose of thioridazine and should be avoided (see Precautions and Contraindications). Caution must be exercised when administering lidocaine as it may increase the risk of developing seizures.

Administration of activated charcoal followed by a saline cathartic may enhance elimination of the drug. Keep patient under observation and maintain an open airway, since involvement of the extrapyramidal mechanism may produce dysphagia and respiratory difficulty in severe overdose.

Induction of emesis should generally not be attempted, since a phenothiazine induced dystonic reaction of the head or neck may result in aspiration of vomitus during emesis.

In severe cases of hypotension, plasma expanders may be used. In resistant cases, a vasopressor agent (e.g. dopamine) may be used, with careful monitoring of blood pressure and cardiac function. In cases of convulsion, intravenous benzodiazepines may be required. Barbiturates must be avoided since they may potentiate phenothiazine-induced respiratory depression.

Attention should be given to symptoms of metabolic acidosis and delayed cardiac effects.

Presentation

Aldazine 10, 10 mg tablet: light green, biconvex, film coated; bottles of 100 - AUST R 17568.

Aldazine 25, 25 mg tablet: light brown, biconvex, film coated, marked "TZ/25" on one side, "α" on reverse; bottles of 100 - AUST R 53177.

Aldazine 50, 50 mg tablet: light green, biconvex, film coated, marked "TZ/50" on one side, "α" on reverse; bottles of 100 - AUST R 17571.

Aldazine 100, 100 mg tablet: dark green, biconvex, film coated, marked "TZ/100" on one side, "α" on reverse; bottles of 100 - AUST R 49813.

(Blister packs of 90 tablets for all strengths are available to hospitals only; 10 mg – AUST R 93654, 25 mg - AUST R 53178, 50 mg – AUST R 17597, 100 mg – AUST R 49814.)

Store below 30°C.

Poison Schedule

S4 - Prescription Only Medicine

Name and Address of the Sponsor

Alphapharm Pty Limited

Chase Building 2

Wentworth Park Road

Glebe NSW 2037

ABN 93 002 359 739

www.alphapharm.com.au

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