For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only

Thioril

1. Generic Name:

Thioridazine

2. Qualitative and quantitative composition:

THIORIL-10

Each film coated tablet contains:

Thioridazine Hydrochloride U.S.P…..10mg

Colours: Lake of Sunset Yellow & Titanium Dioxide I.P.

THIORIL-25

Each film coated tablet contains:

Thioridazine Hydrochloride U.S.P…..25mg

Excipients…….q.s.

Colours: Lake of Indigo Carmoisine, Lake of Ponceau 4R, Lake of Sunset Yellow & Titanium Dioxide I.P.

THIORIL-50

Each film coated tablet contains:

Thioridazine Hydrochloride U.S.P…..50mg

Excipients……q.s.

Colours: Lake of Carmoisine & Titanium Dioxide I.P.

3. Dosage form and strength:

Dosage form: Film Coated tablets

Strength:10, 25, 50 mg Thioridazine hydrochloride

4. Clinical particulars:

4.1 Therapeutic indication:

Thioridazine hydrochloride tablets are indicated for the management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Due to the risk of significant, potentially life threatening, proarrhythmic effects with thioridazine treatment, thioridazine hydrochloride tablets should be used only in patients who have failed to respond adequately to treatment with appropriate courses of 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 thioridazine hydrochloride tablets, 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.

However, the prescriber should be aware that thioridazine hydrochloride tablets have not been systematically evaluated in controlled trials in treatment refractory schizophrenic patients and its efficacy in such patients is unknown.

4.2 Posology and method of administration:

Since thioridazine hydrochloride tablets are 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 individualized and the smallest effective dosage should be determined for each patient Or As directed by the physician.

4.3 Contraindications:

Thioridazine is contra-indicated in patients with:

- Clinically significant cardiac disorders (e.g. cardiac failure, angina, cardiomyopathy or LV dysfunction):
- QTc interval prolongation.
- A history of ventricular arrhythmias or Torsades de Pointes
- Bradycardia or 2nd or 3rd degree heart block
- A family history of QTc interval prolongation
- Uncorrected hypokalaemia or hypomagnesaemia

Prescribers should also note that thioridazine is metabolised by the cytochrome P450 2D6 pathway. Treatment is therefore contraindicated in patients known to have genetically-determined reduced or no activity of cytochrome P450 2D6. Thioridazine is also contraindicated when patients are being prescribed other therapeutic agents known to be either substrates or the inhibitors of cytochrome P450 2D6.

Because thioridazine prolongs the QTc interval in a concentration-related manner, it is also contraindicated with concurrent use of other drugs known to prolong the QTc interval

Thioridazine is also contra-indicated in patients with:

- Hypersensitivity to thioridazine HCl or other phenothiazines, thioridazine base or any of the other excipients.
- A history of hypersensitivity reactions, including severe photosensitivity.
- Comatose states, dementia and severe depression of the CNS.
- History of serious haematological conditions (e.g. bone marrow suppression).

4.4 Special warnings and precautions for use:

<u>Increased Mortality in Elderly Patients with Dementia-Related Psychosis</u>

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Thioridazine hydrochloride is not approved for the treatment of patients with dementia-related psychosis.

<u>Potential for Proarrhythmic Effects</u>

Due to the potential for significant, possibly life threatening, proarrhythmic effects with thioridazine treatment, thioridazine should be reserved for use in the treatment of 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 thioridazine, 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 reported 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.

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 thioridazine therapy has not been established but, given the ability of thioridazine to prolong the QTc interval, such a relationship is possible.

Certain 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, including 1) bradycardia, 2) hypokalemia, 3) concomitant use of other drugs that prolong the QTc interval, 4) presence of congenital prolongation of the QT interval, and 5) for thioridazine in particular, its use in patients with reduced activity of P450 2D6 or its coadministration with drugs that may inhibit P450 2D6 or by some other mechanism interfere with the clearance of thioridazine.

It is recommended that patients being considered for thioridazine treatment have a baseline ECG performed and serum potassium levels measured. Serum potassium should be normalized before initiating treatment and patients with a QTc interval greater than 450 msec should not receive thioridazine treatment. It may also be useful to periodically monitor ECG's and serum potassium during thioridazine treatment, especially during a period of dose adjustment. Thioridazine should be discontinued in patients who are found to have a QTc interval over 500 msec.

Patients taking thioridazine who experience symptoms that may be associated with the occurrence of Torsades de pointes (e.g., dizziness, palpitations, or syncope) may warrant further cardiac evaluation; in particular, Holter monitoring should be considered.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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 antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic

drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do 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 reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

It has been suggested in regard to phenothiazines in general, that people who have demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to one may be more prone to demonstrate a reaction to others. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. Physicians should carefully consider benefit versus risk when treating less severe disorders.

Reproductive studies in animals and clinical experience to date have failed to show a teratogenic effect with thioridazine. However, in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, thioridazine should be given only when the benefits derived from treatment exceed the possible risks to mother and fetus.

Pregnancy

Nonteratogenic Effects

Neonates exposed to antipsychotic drugs, 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. Thioridazine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include, 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Central Nervous System Depressants

As in the case of other phenothiazines, thioridazine is capable of potentiating central nervous system depressants (e.g., alcohol, anesthetics, barbiturates, narcotics, opiates, other psychoactive drugs, etc.) as well as atropine and phosphorus insecticides. Severe respiratory depression and respiratory arrest have been reported when a patient was given a phenothiazine and a concomitant high dose of a barbiturate.

PRECAUTIONS

Leukopenia and/or agranulocytosis and convulsive seizures have been reported but are infrequent. In schizophrenic patients with epilepsy, anticonvulsant medication should be maintained during treatment with thioridazine. Pigmentary retinopathy, which has been observed primarily in patients taking larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; examination of the fundus discloses deposits of pigment. The possibility of this complication may be reduced by remaining within the recommended limits of dosage.

Where patients are participating in activities requiring complete mental alertness (e.g., driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually. Female patients appear to have a greater tendency to orthostatic hypotension than male patients. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension in view of the fact that phenothiazines may induce a reversed epinephrine effect on occasion. Should a vasoconstrictor be required, the most suitable are levarterenol and phenylephrine.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. 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. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies reported to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

4.5 Drug-Interaction:

Reduced cytochrome P450 2D6 isozyme activity, drugs which inhibit this isozyme (e.g., fluoxetine and paroxetine), and certain other drugs (e.g., fluvoxamine, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine. 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 result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is 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.

Drugs That Inhibit Cytochrome P450 2D6

In a reported 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 Cmax and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P450 2D6 isozyme activity. Thus, this reported study suggests that drugs that inhibit P450 2D6 or the presence of reduced activity

levels of this isozyme will produce elevated plasma levels of thioridazine. Therefore, the coadministration 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 b.i.d. for one week) on thioridazine steady-state concentration was evaluated in ten male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased 3-fold following coadministration of fluvoxamine. Fluvoxamine and thioridazine should not be coadministered.

Propranolol

Concurrent administration of propranolol (100 mg to 800 mg daily) has been reported to produce increases in plasma levels of thioridazine (approximately 50% to 400%) and its metabolites (approximately 80% to 300%). Propranolol and thioridazine should not be coadministered.

Pindolol

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

Drugs That Prolong the QTc Interval

There are no studies of the coadministration of thioridazine and other drugs that prolong the QTc interval. However, it is expected that such coadministration would produce additive prolongation of the QTc interval and, thus, such use is contraindicated.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy:

It is not recommended to take Thioridazine at the time of pregnancy.

Nursing woman:

Phenothiazines cause galactorrhea in 26 to 40% of female patients. Hyperprolactinemia appears to be the cause of the galactorrhea. There is some evidence that thioridazine increases serum prolactin to a greater extent than other phenothiazines. The hyperprolactinemia is caused by the drug's dopamine-blocking action in the tuberoinfundibular pathway. The prolactin level in a mother with established lactation may not affect her ability to breastfeed.

Adults

The usual starting dose for adult schizophrenic patients is 50 mg to 100 mg three times a day, with a gradual increment to a maximum of 800 mg daily if necessary. Once effective control of symptoms has been achieved, the dosage may be reduced gradually to determine the minimum maintenance dose. The total daily dosage ranges from 200 mg to 800 mg, divided into two to four doses.

Pediatric Patients

For pediatric patients with schizophrenia who are unresponsive to other agents, the recommended initial dose is 0.5 mg/kg/day given in divided doses. Dosage may be increased gradually until optimum therapeutic effect is obtained or the maximum dose of 3 mg/kg/day has been reached.

4.7 Effects on ability to drive and use machines:

Thioridazine Accord has no direct influence on the ability to drive and use machines but may cause seizure in some cases.

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 **Undesirable effects**

In the recommended dosage ranges with thioridazine hydrochloride most side effects are mild and transient.

Central Nervous System

Drowsiness may be encountered on occasion, especially where large doses are given early in treatment. Generally, this effect tends to subside with continued therapy or a reduction in dosage. Pseudoparkinsonism and other extrapyramidal symptoms may occur but are infrequent. Nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache have been reported but are extremely rare.

Autonomic Nervous System

Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor have been seen.

Endocrine System

Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema have been described.

Skin

Dermatitis and skin eruptions of the urticarial type have been observed infrequently.

Photosensitivity is extremely rare.

Cardiovascular System

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 thioridazine 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.

Other Rare cases described as parotid swelling have been reported following administration of thioridazine.

Post Introduction Reports

These are voluntary reports of adverse events temporally associated with thioridazine that were received since marketing, and there may be no causal relationship between thioridazine use and these events: priapism.

Phenothiazine Derivatives

It should be noted that efficacy, indications, and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines. The most

common neurological side effects in these patients are parkinsonism and akathisia. There appears to be an increased risk of agranulocytosis and leukopenia in the geriatric population. 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:

Autonomic Reactions***:*** Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis. ***Blood Dyscrasias:*** Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity***:*** Jaundice, biliary stasis.

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

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of antipsychotics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the WARNINGS section and subsequently.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk, and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with antipsychotics is withheld. It is generally believed that reversibility is more likely after short rather than long-term antipsychotic 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 antipsychotic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for antipsychotic drugs may mask the signs of the syndrome.

Neuroleptic Malignant Syndrome (NMS): Chronic use of antipsychotics may be associated with the development of Neuroleptic Malignant Syndrome. The salient features of this syndrome are described in the WARNINGS section and subsequently. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term

treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose:

Many of the symptoms observed are extensions of the side effects 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 because of the risk of delayed effects.

Signs and Symptoms

Effects and clinical complications of acute overdose involving phenothiazines may include:

Cardiovascular: Cardiac arrhythmias, hypotension, shock, ECG changes, increased QT and PR intervals, non-specific ST and T wave changes, bradycardia, sinus tachycardia, atrioventricular block, ventricular tachycardia, ventricular fibrillation, Torsades de pointes, myocardial depression.

Central Nervous System: Sedation, extrapyramidal effects, confusion, agitation, hypothermia, hyperthermia, restlessness, seizures, areflexia, coma.

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

Respiratory: Respiratory depression, apnea, pulmonary edema.

Gastrointestinal: Hypomotility, constipation, ileus.

Renal: Oliguria, uremia.

Toxic dose and blood concentration ranges for the phenothiazines have not been firmly established. It has been suggested that the toxic blood concentration range for thioridazine begins at 1 mg/dL, and 2 to 8 mg/dL is the lethal concentration range.

Treatment

An airway must be established and maintained. Adequate oxygenation and ventilation must be ensured.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Treatment may include one or more of the following therapeutic 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 overdosage of thioridazine and should be avoided. Caution must be exercised when administering lidocaine, as it may increase the risk of developing seizures.

Treatment of hypotension may require intravenous fluids and vasopressors. Phenylephrine, levarterenol, or metaraminol are the appropriate pressor agents for use in the management of refractory hypotension. The potent α adrenergic blocking properties of the phenothiazines makes the use of vasopressors with mixed α and β adrenergic agonist properties inappropriate, including epinephrine

and dopamine. Paradoxical vasodilation may result. In addition, it is reasonable to expect that adrenergic-blocking properties of bretylium might be additive to those of thioridazine, resulting in problematic hypotension.

In managing overdosage, the physician should always consider the possibility of multiple drug involvement. Gastric lavage and repeated doses of activated charcoal should be considered. Induction of emesis is less preferable to gastric lavage because of the risk of dystonia and the potential for aspiration of vomitus. Emesis should not be induced in patients expected to deteriorate rapidly, or those with impaired consciousness.

Acute extrapyramidal symptoms may be treated with diphenhydramine hydrochloride or benztropine mesylate.

Avoid the use of barbiturates when treating seizures, as they may potentiate phenothiazine-induced respiratory depression.

Forced diuresis, hemoperfusion, hemodialysis and manipulation of urine pH are of unlikely benefit in the treatment of phenothiazine overdose due to their large volume of distribution and extensive plasma protein binding.

5. Pharmacological properties:

5.1 Mechanism of Action:

Thioridazine, work to treat psychosis is act by blocking dopamine (DA) receptors. These medications effectively treat the positive symptoms of schizophrenia, such as hallucinations, delusions, and disorganization. Positive symptoms are believed to manifest as a result of increased levels of dopamine in the mesolimbic pathway. Thioridazine blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain; blocks alpha-adrenergic effect, depresses the release of hypothalamic and hypophyseal hormones and is believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis. More specifically, thioridazine blocks DA-2 receptors in the mesolimbic pathway, diminishing positive symptoms. Thioridazine is classified as a low potency first-generation antipsychotic, and as such, is relatively sedating. Thioridazine is a substrate of the hepatic enzyme CYP450 2D6 and is also an inhibitor of the same enzyme.

5.2 **Pharmacodynamic properties:**

Thioridazine is a trifluoro-methyl phenothiazine derivative intended for the management of schizophrenia and other psychotic disorders. Thioridazine has not been shown effective in the management of behaviorial complications in patients with mental retardation. Thioridazine blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain; blocks alpha-adrenergic effect, depresses the release of hypothalamic and hypophyseal hormones and is believed to depress the reticular activating system thus affecting basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis.

5.3 Pharmacokinetic properties:

Absorption

Thirol is rapidly absorbed with maximum plasma concentrations (Cmax) occurring approximately 1-2 hours after tablet intake. The absolute bioavailability is 42% (range 15−76%), and dose proportional increases in exposure (AUC and Cmax) are observed between the 30 and 60 mg dose strengths. Following multiple doses, AUC values for both Thioril and the active metabolite increase by approximately 50% when compared to single dose AUC values. Ingestion of a high fat meal modestly reduced the Cmax (by 10%) and modestly increased the AUC (by 12%) of Thioril and slightly delayed

the time for Thioril to reach peak concentrations. These changes are not clinically significant. Priligy can be taken with or without food.

Distribution

More than 99% of Thioril is bound in vitro to human serum proteins. The active metabolite is 98.5% protein bound. Thioril has a mean steady state volume of distribution of 162 L.

Biotransformation

In vitro studies suggest that Thioril is cleared by multiple enzyme systems in the liver and kidneys, primarily CYP2D6, CYP3A4, and flavin monooxygenase (FMO1). Following oral dosing of 14C−Thioril, Thioril was extensively metabolized to multiple metabolites primarily through the following biotransformational pathways: N−oxidation, N−demethylation, naphthyl hydroxylation, glucuronidation and sulfation. There was evidence of presystemic first−pass metabolism after oral administration. Intact Thioril and Thioril−N−oxide were the major circulating moieties in the plasma. In vitro binding and transporter studies show that Thioril−N−oxide is inactive. Additional metabolites including desmethylThioril and didesmethylThioril account for less than 3% of the total circulating drug –related materials in plasma. In vitro binding studies indicate that DED is equipotent to Thioril and didesmethylThioril has approximately 50% of the potency of Thioril (see section 5.1). The unbound exposures (AUC and Cmax) of DED are approximately 50% and 23%, respectively, of the unbound exposure of Thioril.

Elimination

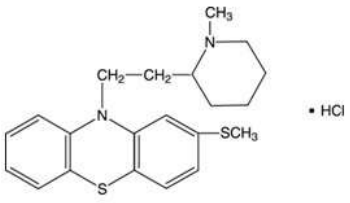
The metabolites of Thioril were primarily eliminated in the urine as conjugates. Unchanged active substance was not detected in the urine. Following oral administration, Thioril has an initial (disposition) half-life of approximately 1.5 hours, with plasma levels less than 5% of peak concentrations by 24 hours post-dose, and a terminal half-life of approximately 19 hours. The terminal half−life of DED is approximately 19 hours.

6. Nonclinical properties:

A full assessment of the reported safety pharmacology, repeat dose toxicology, genetic toxicology, carcinogenicity, dependence/withdrawal liability, phototoxicity and developmental reproductive toxicology of Thioril was conducted in preclinical species (mouse, rat, rabbit, dog and monkey) up to the maximum tolerated doses in each species. Due to the more rapid bioconversion in the preclinical species than in man, pharmacokinetic exposure indices (Cmax and AUC0−24 hr) at the maximum tolerated doses in some studies approached those observed in man. However, the body weight normalized dose multiples were greater than 100-fold. There were no clinically relevant safety hazards identified in any of these studies. In studies with oral administration, Thioril was not carcinogenic to rats when administered daily for approximately two years at doses up to 225 mg/kg/day, yielding approximately twice the exposures (AUC) seen in human males given the Maximum Recommended Human Dose (MRHD) of 60 mg. Thioril also did not cause tumors in Tg.rasH2 mice when administered at the maximum possible doses of 100 mg/kg for 6 months and 200 mg/kg for 4 months. The steady state exposures of Thioril in mice following 6-months oral administration at 100 mg/kg/day were less than the single dose exposures observed clinically at 60 mg.

Description:

Thioridazine hydrochloride is 2-methylmercapto-10-[2-(N-methyl-2-piperidyl) ethyl] phenothiazine. Its structural formula, molecular weight (M.Wt.: 407.05) and molecular formula ($C_{21}H_{26}N_2S_2 \bullet HCl$) are:



Thioridazine hydrochloride, is available as tablets for oral administration containing 10 mg, 25 mg, 50 mg.

7. Pharmaceutical particulars:

8.1 Incompatibilities:

Not applicable.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

THIORIL-10, THIORIL-25 and THIORIL-50 are available as Blister Strip of 10 Tablets

8.4 Storage and handing instructions:

Store at a Temperature Not Exceeding 30°C, Protected From Light And Moisture.

9. Patient Counselling Information

THIORIL

Thioridazine tablets

Package leaflet: Information for the user

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What THIORIL is and what it is used for

Thioridazine hydrochloride is 2-methylmercapto-10-[2-(N-methyl-2-piperidyl) ethyl] phenothiazine. Thioridazine hydrochloride tablets are indicated for the management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Due to the risk of significant, potentially life threatening, proarrhythmic effects with thioridazine treatment, thioridazine hydrochloride tablets should be used only in patients who have failed to respond adequately to treatment with appropriate courses of 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 thioridazine hydrochloride tablets, 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.

9.2 What you need to know before you take THIORIL

Do not take THIORIL:

- If any Clinically significant cardiac disorders (e.g. cardiac failure, angina, cardiomyopathy or LV dysfunction):
- If QTc interval prolongation.
- If A history of ventricular arrhythmias or Torsades de Pointes
- If Bradycardia or 2nd or 3rd degree heart block
- If A family history of QTc interval prolongation
- If Uncorrected hypokalaemia or hypomagnesaemia
- If Hypersensitivity to thioridazine HCl or other phenothiazines, thioridazine base or any of the other excipients.
- If A history of hypersensitivity reactions, including severe photosensitivity.
- If Comatose states, dementia and severe depression of the CNS.
- If History of serious haematological conditions (e.g. bone marrow suppression).

Warnings and precautions

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Thioridazine hydrochloride is not approved for the treatment of patients with dementia-related psychosis.

Potential for Proarrhythmic Effects

Due to the potential for significant, possibly life threatening, proarrhythmic effects with thioridazine treatment, thioridazine should be reserved for use in the treatment of 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 thioridazine, 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 reported 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.

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 thioridazine therapy has not been established but, given the ability of thioridazine to prolong the QTc interval, such a relationship is possible.

Certain 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, including 1) bradycardia, 2) hypokalemia, 3) concomitant use of other drugs that prolong the QTc interval, 4) presence of congenital prolongation of the QT interval, and 5) for thioridazine in particular, its use in patients with reduced activity of P450 2D6 or its coadministration with drugs that may inhibit P450 2D6 or by some other mechanism interfere with the clearance of thioridazine.

It is recommended that patients being considered for thioridazine treatment have a baseline ECG performed and serum potassium levels measured. Serum potassium should be normalized before initiating treatment and patients with a QTc interval greater than 450 msec should not receive thioridazine treatment. It may also be useful to periodically monitor ECG's and serum potassium during thioridazine treatment, especially during a period of dose adjustment. Thioridazine should be discontinued in patients who are found to have a QTc interval over 500 msec.

Patients taking thioridazine who experience symptoms that may be associated with the occurrence of Torsades de pointes (e.g., dizziness, palpitations, or syncope) may warrant further cardiac evaluation; in particular, Holter monitoring should be considered.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

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 antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do 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 reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

It has been suggested in regard to phenothiazines in general, that people who have demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to one may be more prone to demonstrate a reaction to others. Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. Physicians should carefully consider benefit versus risk when treating less severe disorders.

Reproductive studies in animals and clinical experience to date have failed to show a teratogenic effect with thioridazine. However, in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, thioridazine should be given only when the benefits derived from treatment exceed the possible risks to mother and fetus.

Pregnancy

Nonteratogenic Effects

Neonates exposed to antipsychotic drugs, 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. Thioridazine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include, 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Central Nervous System Depressants

As in the case of other phenothiazines, thioridazine is capable of potentiating central nervous system depressants (e.g., alcohol, anesthetics, barbiturates, narcotics, opiates, other psychoactive drugs, etc.) as well as atropine and phosphorus insecticides. Severe respiratory depression and respiratory arrest

have been reported when a patient was given a phenothiazine and a concomitant high dose of a barbiturate.

PRECAUTIONS

Leukopenia and/or agranulocytosis and convulsive seizures have been reported but are infrequent. In schizophrenic patients with epilepsy, anticonvulsant medication should be maintained during treatment with thioridazine. Pigmentary retinopathy, which has been observed primarily in patients taking larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; examination of the fundus discloses deposits of pigment. The possibility of this complication may be reduced by remaining within the recommended limits of dosage.

Where patients are participating in activities requiring complete mental alertness (e.g., driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually. Female patients appear to have a greater tendency to orthostatic hypotension than male patients. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension in view of the fact that phenothiazines may induce a reversed epinephrine effect on occasion. Should a vasoconstrictor be required, the most suitable are levarterenol and phenylephrine.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. 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. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies reported to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Reduced cytochrome P450 2D6 isozyme activity, drugs which inhibit this isozyme (e.g., fluoxetine and paroxetine), and certain other drugs (e.g., fluvoxamine, propranolol, and pindolol) appear to appreciably inhibit the metabolism of thioridazine. 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 result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is 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.

Drugs That Inhibit Cytochrome P450 2D6

In a reported 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 2.4fold higher Cmax and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P450 2D6 isozyme activity. Thus, this reported study suggests that drugs that inhibit P450 2D6 or the presence of reduced activity levels of this isozyme will produce elevated plasma levels of thioridazine. Therefore, the coadministration 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 b.i.d. for one week) on thioridazine steady-state concentration was evaluated in ten male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased 3-fold following coadministration of fluvoxamine. Fluvoxamine and thioridazine should not be coadministered.

Propranolol

Concurrent administration of propranolol (100 mg to 800 mg daily) has been reported to produce increases in plasma levels of thioridazine (approximately 50% to 400%) and its metabolites (approximately 80% to 300%). Propranolol and thioridazine should not be coadministered.

Pindolol

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

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 and, thus, such use is contraindicated.

9.3 How to take THIORIL

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is **one tablet once a day with food**. Treatment should continue for as long as your doctor tells you. Usually this is for at least 6 to 12 months and may be for many years.

If you take more THIORIL than you should

If you accidentally take more than the recommended dose of THIORIL you may be at increased risk of experiencing possible side effects with this medicine

Contact your doctor or nearest emergency department immediately for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take THIORIL

It is important not to miss a dose of THIORIL. If you do miss a dose, work out how long since you should have taken it.

- **If it is less than 18 hours** after you usually take THIORIL, take it as soon as you can, and then take your next dose at its regular time.
- **If it is more than 18 hours** after you usually take THIORIL, then do not take the missed dose. Wait and take the next dose at the regular time. **Do not take a double dose** to make up for a forgotten tablet.

If you are sick (vomit) less than 1 hour after taking THIORIL, take another tablet. You do not need to take another tablet if you are sick (vomit) more than 1 hour after taking THIORIL.

If you stop taking THIORIL

Do not stop taking THIORIL without your doctor's advice. **Talk to your doctor** before you stop taking THIORIL for any reason, particularly if you are experiencing any side effects or you have another

illness.

- **Tell your doctor immediately** about new or unusual symptoms after you stop treatment.
- Particularly symptoms you associate with some specific disorder.
- **Talk to your doctor** before you restart taking THIORIL tablets.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist

9.4 Possible side effects

In the recommended dosage ranges with thioridazine hydrochloride most side effects are mild and transient.

Central Nervous System

Drowsiness may be encountered on occasion, especially where large doses are given early in treatment. Generally, this effect tends to subside with continued therapy or a reduction in dosage. Pseudoparkinsonism and other extrapyramidal symptoms may occur but are infrequent. Nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache have been reported but are extremely rare.

Autonomic Nervous System

Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor have been seen.

Endocrine System

Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema have been described.

Skin

Dermatitis and skin eruptions of the urticarial type have been observed infrequently.

Photosensitivity is extremely rare.

Cardiovascular System

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 thioridazine 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.

Other Rare cases described as parotid swelling have been reported following administration of thioridazine.

Post Introduction Reports

These are voluntary reports of adverse events temporally associated with thioridazine that were received since marketing, and there may be no causal relationship between thioridazine use and these events: priapism.

Phenothiazine Derivatives

It should be noted that efficacy, indications, and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines. The most common neurological side effects in these patients are parkinsonism and akathisia. There appears to be an increased risk of agranulocytosis and leukopenia in the geriatric population. 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:

Autonomic Reactions***:*** Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis, Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

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

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of antipsychotics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the WARNINGS section and subsequently.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk, and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with antipsychotics is withheld. It is generally believed that reversibility is more likely after short rather than long-term antipsychotic 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 antipsychotic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for antipsychotic drugs may mask the signs of the syndrome.

Neuroleptic Malignant Syndrome (NMS): Chronic use of antipsychotics may be associated with the development of Neuroleptic Malignant Syndrome. The salient features of this syndrome are described in the WARNINGS section and subsequently. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities

of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

Withdrawal symptoms

Stopping taking thioril suddenly may cause withdrawal symptoms. These include, shakes (tremors), sweating, agitation, problems sleeping, anxiety (sometimes severe), headaches, muscle pain, tension, restlessness, confusion, irritability and fits (epileptic seizures). In severe cases the following effects may happen: a feeling of being unreal, oversensitivity to noise, light and touch, numbness and tingling of the hands and feet or hallucinations. Gradual withdrawal will help to reduce these effects.

What is the most important information I should know about THIORIL?

- THIORIL contains thioridazine hydrochloride which can cause severe drowsiness, breathing problems (respiratory depression), coma, and death when taken with opioid medicines.
- THIORIL can make you sleepy or dizzy and can slow your thinking and motor skills. This may get better over time.
- Do not drive, operate heavy machinery, or do other dangerous activities until you know how THIORIL affects you.
- THIORIL may cause problems with your coordination, especially when you are walking or picking things up.

Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking THIORIL until you talk to your healthcare provider.

When taken with alcohol or drugs that cause sleepiness or dizziness, THIORIL may make your sleepiness or dizziness worse.

THIORIL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worse anxiety
- trouble sleeping (insomnia)
- acting on dangerous impulses
- attempts to commit suicide
- feeling agitated or restless
- new or worse irritability
- an extreme increase in activity and talking (mania)
- new or worse depression
- panic attacks of acting aggressive, being angry, or violent
- other unusual changes in behaviour or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviours, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms. Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

Do not stop THIORIL without first talking to a healthcare provider.

- Stopping THIORIL suddenly can cause serious problems. Stopping THIROL suddenly can cause seizures that will not stop in some cases.

9.5 How to store THIORIL

Store at a Temperature Not Exceeding 30°C, Protected From Light And Moisture.

9.6 Contents of the pack and other information

THIORIL-10, THIORIL-25 and THIORIL-50 are available as Blister Strip of 10 Tablets

What THIORIL contains

- The active substance is **Thioridazine Hydrochloride.**

10. Details of manufacturer

M/S. GKM NEW PHARMA
Spl. Type Plot No. 5,6,7,8
PIPDIC Electronic Park,
Thirubuvanai,
Puducherry- 605 107

11. Details of permission or licence number with date

Mfg Lic. No. M/205/2012 issued on 09 Feb. 2018

12. Date of revision

MAY 2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/THIORIL 10, 25, 50 mg/MAY-21/02/PI