

MELLERIL[®]**International Package Leaflet**

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MELLERIL[®] 10 mg, 25 mg, 50 mg and 100 mg FILM-COATED TABLETS

MELLERIL[®] 30 mg and 200 mg PROLONGED-RELEASE TABLETS

MELLERIL[®] 3% ORAL DROPS, SOLUTION

MELLERIL[®] 0.5% ORAL SUSPENSION

Neuroleptic agent.

COMPOSITION AND PHARMACEUTICAL FORM

Melleril film-coated tablets: The active ingredient is thioridazine hydrochloride. One film-coated tablet contains 10 mg, 25 mg, 50 mg or 100 mg thioridazine hydrochloride.

Melleril prolonged-release tablets, scored: The active ingredient is thioridazine hydrochloride. One prolonged-release tablet contains 30 mg or 200 mg thioridazine hydrochloride.

Melleril oral drops, solution: The active ingredient is thioridazine hydrochloride. 1 mL (= 30 drops) contains 30 mg thioridazine hydrochloride (1 drop = 1 mg).

Melleril oral suspension: The active ingredient is thioridazine base. 1 mL of the 0.5% suspension contains 5 mg thioridazine base.

Certain dosage strengths and pharmaceutical forms may not be available in all countries.

INDICATIONS

Melleril should be used only in adult patients with chronic schizophrenia or acute exacerbations 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.

DOSAGE AND ADMINISTRATION

Before initiating treatment with Melleril, baseline ECG must be performed to exclude patients with relevant pre-existing cardiovascular disease (see "CONTRAINDICATIONS").

Dosage and timing of drug intake should be individually adjusted according to the nature and severity of symptoms. It is recommended that the initial dose should be at the lower end of the ranges mentioned below and be gradually increased until the fully effective level is reached. The total daily amount is usually given in 2 to 4 divided doses.

Melleril prolonged-release tablets should not be chewed.

Schizophrenia and acute exacerbations

- **Acute exacerbations in hospitalized psychotic adults:** 100-600 mg/day up to a maximum of 800 mg/day.

- **Chronic schizophrenia:** 100-600 mg/day in institutionalized patients; 50-300 mg/day in out-patients.

In underweight patients, in patients with impaired renal or hepatic function, a particularly low initial dosage followed by small increments is recommended.

Usually 2 to 3 weeks or more are required to demonstrate unequivocal positive effects in hospitalized schizophrenics. Maximum benefit may require 6 weeks to 6 months to develop in chronically psychotic patients. In contrast, improvement of acutely psychotic patients may be seen within 24 to 48 hours.

Optimal dosage of antipsychotic drugs is sometimes difficult to determine and flexible therapy with dosage adjustments to changing clinical requirements may be needed. This can also help to reduce the incidence of side effects.

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 dyskinesic signs. These may falsely presage the onset of a depressive or psychotic episode.

CONTRAINDICATIONS

Hypersensitivity to thioridazine hydrochloride, thioridazine base, or any of the excipients.

Comatose states or severe depression of the central nervous system.

History of serious haematological conditions (e.g. bone marrow depression).

History of hypersensitivity reactions, such as severe photosensitivity or hypersensitivity to other phenothiazines.

Severe cardiac disorders, especially clinically relevant arrhythmias, e.g. torsade de pointes, congenital long QT syndrome.

Co-medication with drugs known to prolong the QTc interval.

Co-medication with selective serotonin reuptake inhibitors (SSRIs) or other drugs metabolised by the cytochrome P450 2D6 isozyme (see "INTERACTIONS").

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

Extrapyramidal disorders

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. Although the risk with thioridazine appears to be relatively low and is virtually absent at the lower dose level, extrapyramidal symptoms may occur, especially with high (neuroleptic) doses of Melleril.

Tardive dyskinesia

There have been rare reports of tardive dyskinesia in patients receiving thioridazine. Although no clear association between development of this syndrome and the duration of antipsychotic drug treatment has been shown, discontinuation or reduction to the minimum effective dose should be considered in patients who develop signs and symptoms of tardive dyskinesia during Melleril therapy. Such symptoms can become gradually worse or even occur after discontinuation of treatment.

Neuroleptic Malignant Syndrome (NMS)

This syndrome has been reported in very rare cases in association with thioridazine. NMS is a potentially fatal disorder characterized by muscular rigidity, hyperthermia, altered consciousness and autonomic dysfunction (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

In cases where NMS develops and in patients with unexplained high fever without additional clinical manifestations of NMS, Melleril must be discontinued.

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

Seizure threshold

Many neuroleptic drugs, including thioridazine, can lower the seizure threshold and induce discharge patterns in the EEG that are associated with epileptic seizure disorders.

Cardiovascular disease

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, congenital long QT syndrome, or circulatory lability (see "CONTRAINDICATIONS"). Before initiating treatment with Melleril, baseline ECG has to be performed to exclude patients with relevant pre-existing cardiovascular disease (see "CONTRAINDICATIONS"). Increases in the QT interval, cardiac arrest, cardiac arrhythmias and very rarely torsade de pointes arrhythmia have been reported in association with thioridazine; isolated cases have been fatal. These changes are usually confined to high doses, and are more likely to occur when potassium blood levels are low. Occasional reports have implicated phenothiazine therapy in some cases of sudden death. Although such retrospective cases are difficult to interpret, isolated cases of sudden death in apparently healthy young individuals may be directly attributable to cardiac arrhythmias following treatment with thioridazine.

Precautions

Anticholinergic properties: On account of its anticholinergic properties, Melleril should be used with caution in patients with a history of increased intraocular pressure, narrow-angle glaucoma, urinary retention (e.g. prostatic hypertrophy) and chronic constipation.

Liver disorders: In patients with liver disease regular monitoring of liver function is necessary.

Blood dyscrasias: Although only rare cases of leucopenia or agranulocytosis have been reported in association with Melleril, as with any phenothiazine therapy, blood counts should be carried out regularly during the first three to four months of treatment and should be performed immediately whenever clinical signs suggestive of blood dyscrasia occur.

Blood pressure: Orthostatic hypotension is frequently observed in patients taking thioridazine. When starting treatment with Melleril it is advisable to check blood pressure, especially in the elderly and in patients with postural hypotension or a labile circulation.

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.

Tolerance: 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 (see "DOSAGE AND ADMINISTRATION")

INTERACTIONS

Pharmacokinetic interactions

Cytochrome P450 2D6 metabolism: Thioridazine is metabolized by P450 2D6 and is itself an inhibitor of this pathway. The effects of thioridazine may therefore be increased and prolonged by drugs which inhibit this P450 isoform, such as cimetidine, fluoxetine, paroxetine, other SSRIs, moclobemide. Co-medication with those drugs is contraindicated (see "CONTRAINDICATIONS").

Tricyclic antidepressants: Co-medication with drugs metabolised by the P450 2D6 isozyme is contraindicated (see "CONTRAINDICATIONS"). Co-medication results in increased plasma levels of tricyclic antidepressants and/or phenothiazines. As a result cardiac arrhythmias have been reported in patients taking thioridazine and tricyclic antidepressants concomitantly.

Antipsychotics: Co-medication with drugs metabolised by the P450 2D6 isozyme is contraindicated (see "CONTRAINDICATIONS").

Antiepileptics: Phenothiazines, including thioridazine, may lower the seizure threshold. Serum levels of phenytoin may be raised or lowered by the use of thioridazine, and dosage adjustment may be necessary. Concomitant use with carbamazepine was found to have no effect on serum level of either thioridazine or carbamazepine.

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

Antihypertensives and β -blockers: As a result of inhibition of metabolism, co-medication with phenothiazines may cause increased plasma concentrations of each medication, possibly resulting in severe hypotension, cardiac arrhythmias or CNS side effects (see also above "Cytochrome P450 2D6 metabolism").

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

Pharmacodynamic interactions

CNS depressants: Phenothiazines may potentiate the effects of alcohol and other CNS depressant substances such as benzodiazepines, maprotiline or general anaesthetics.

MAO inhibitors: Concurrent use may prolong and intensify the sedative and anticholinergic effects of either the MAO inhibitor or the phenothiazines.

Lithium: Severe neurotoxic complications, extrapyramidal side effects and sleep-walking episodes have been described in patients concurrently treated with lithium and phenothiazines, including thioridazine.

Anticholinergic agents: Concurrent use 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 Melleril is given concomitantly with drugs such as antihistamines, tricyclic antidepressants or atropine-like compounds.

Antiparkinsonian agents: The effects of both levodopa and Melleril may be inhibited when these drugs are used concomitantly.

Adrenergic vasoconstrictors: Owing to their adrenolytic action, phenothiazines may reduce the pressor effect of adrenergic vasoconstrictors (i.e. ephedrine, phenylephrine).

Quinidine: Concurrent administration with thioridazine can lead to additive myocardial depression.

Antiarrhythmics / prolongation of the QT interval: Since phenothiazines, including Melleril, can induce ECG changes such as prolongation of the QT interval, co-medication with other drugs known to prolong the QTc interval is contraindicated (see "CONTRAINDICATIONS").

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

Antidiabetics: Phenothiazines affect carbohydrate metabolism and may therefore interfere with control of diabetic patients.

Antacids, anti-diarrhoeal agents: These drugs may reduce the gastrointestinal absorption of orally administered phenothiazines.

PREGNANCY AND LACTATION

There have been no adequate and well controlled studies in pregnant women. Embryotoxicity studies in animals have failed to show a teratogenic effect of Melleril (thioridazine). The drug should be used during pregnancy only if the potential benefits to the mother outweigh the possible risks to the fetus.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients receiving Melleril should be warned that blurred vision, drowsiness and other CNS symptoms (see sections “SPECIAL WARNINGS AND PRECAUTIONS FOR USE ” and “UNDESIRABLE EFFECTS”) may occur, in which cases they should not drive, operate machinery or perform any other activities requiring alertness. Patients should also be warned that alcohol or other drugs may potentiate these effects (see “INTERACTIONS”).

UNDESIRABLE EFFECTS

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 $< 0.01\%$.

Like other phenothiazines, the side effects of Melleril are dose dependent and usually represent exaggerated pharmacological effects. The adverse events mentioned below have been reported with Melleril. Most are mild and transient within the recommended dosage ranges. Those that are more severe have mainly been observed at high doses; at lower doses their frequency is very low and side effects such as extrapyramidal symptoms or blood disorders are very rare.

Central nervous system

Very common: sedation and drowsiness.

Common: dizziness.

Uncommon: confusion, agitation, hallucinations, irritability, headache.

Rare: pseudoparkinsonism, convulsions, extrapyramidal symptoms (tremor, muscle rigidity, akathisia, dyskinesia, dystonia), hyperkinesia, tardive dyskinesia.

Very rare: depression, insomnia, nightmares, psychotic reactions, neuroleptic malignant syndrome.

Note: For further details on extrapyramidal symptoms, tardive dyskinesia and neuroleptic malignant syndrome see “SPECIAL WARNINGS AND PRECAUTIONS FOR USE ”.

Autonomic nervous system / anticholinergic effects

Common: dry mouth, blurred vision, disturbances of accommodation, nasal congestion.

Uncommon: nausea, vomiting, diarrhoea, constipation, loss of appetite, urinary retention or incontinence.

Rare: pallor, tremor.

Very rare: paralytic ileus.

Cardiovascular system

Common: orthostatic hypotension.

Uncommon: ECG changes such as prolongation of the QT interval, tachycardia.

Rare: arrhythmias.

Very rare: torsades de pointes and cardiac arrest, both of which may result in death, and sudden death.

Note: See sections “CONTRAINDICATIONS” and “SPECIAL WARNINGS AND PRECAUTIONS FOR USE” for further details on cardiovascular disease.

Endocrine system

Common: galactorrhoea.

Uncommon: amenorrhoea, menstrual irregularities, weight change, disturbances of erection, inhibition of ejaculation.

Rare: priapism.

Very rare: breast engorgement, peripheral oedema.

Blood

Rare: leucopenia, agranulocytosis, thrombocytopenia.

Very rare: anaemia, leukocytosis.

Liver

Uncommon: abnormalities of liver enzymes.

Rare: hepatitis.

Skin

Rare: dermatitis, skin eruptions, urticaria, allergic skin rashes, photosensitivity.

Other

Rare: parotid swelling, hyperthermia, respiratory depression.

Rare cases of pigmentary retinopathy have been reported after long-term treatment, mostly in patients who received doses exceeding the recommended maximum dose of 800 mg/day.

OVERDOSE

Symptoms

Dry mouth, nausea, vomiting, paralytic ileus, nasal congestion, urinary retention, blurred vision, rhabdomyolysis, sedation, confusion, agitation, drowsiness, disorientation, extrapyramidal effects, hyperkinesia, hyperthermia, convulsions, coma.

Torsades de pointes, cardiac arrhythmia, cardiac arrest, tachycardia, severe hypotension, collapse, death.

Respiratory depression, respiratory arrest, pulmonary oedema.

Treatment

Administration of high doses of activated charcoal is recommended but gastric lavage* may also be considered. Induction of emesis should be avoided due to the risk of dystonic reactions and the potential for aspiration of vomitus.

Supportive, symptomatic measures with careful monitoring of the cardiovascular, respiratory, and central nervous systems.

Treatment of hypotension may require intravenous fluids and vasopressors. The potent α -adrenergic blocking properties of the phenothiazine make the use of vasopressors with mixed α - and β -adrenergic agonist properties, including adrenaline and dopamine, inappropriate. Paradoxical vasodilation and hypotension may result.

In the event of convulsions, barbiturates must be avoided, since they may potentiate phenothiazine - induced respiratory depression.

* Note: In cases of acute overdosage with Melleril 200 mg retard tablets use the stomach tube with the largest possible lumen.

PHARMACODYNAMICS

The active substance of Melleril is thioridazine, which belongs to the phenothiazine class of drugs.

The basic pharmacological profile of thioridazine is similar to that of other phenothiazines, but there are significant differences in the clinical spectrum as compared with other agents of the phenothiazine class. The distinctive features of Melleril are its low propensity to cause extrapyramidal side effects (EPS) and its relatively strong sedative and anxiolytic, moderate hypotensive and low antiemetic activities.

Melleril is a neuroleptic effective in controlling severe symptoms of schizophrenia.

PHARMACOKINETICS

Absorption

Thioridazine is rapidly absorbed from the gastrointestinal tract. Maximum plasma concentrations are reached 2-4 hours after ingestion. Mean systemic bioavailability is approximately 60% and there is considerable inter-patient variability in exposure.

With Melleril prolonged release tablets, absorption is prolonged, maximum plasma concentrations being obtained 2-4 hours later than with the non-retarded forms.

Distribution

Protein binding is high (more than 95%) and the compound has a relative distribution volume of 10 L/kg.

Thioridazine crosses the placenta and passes into breast milk. Thioridazine and its major metabolites (sulphoridazine and mesoridazine) cross the blood/brain barrier and can be detected in the cerebro-spinal fluid (CSF). The CSF-to-plasma concentration ratios of the two metabolites are higher than that of the parent compound, indicating that both contribute significantly to the antipsychotic activity of the drug.

Biotransformation

Thioridazine is extensively oxidized in the liver by cytochrome P450 2D6. It is metabolized mainly to a side-chain sulphoxide (mesoridazine) and a side-chain sulphone (sulphoridazine), which possess pharmacodynamic properties similar to those of the parent compound, to a non-psychotic ring sulphoxide which has cardiovascular effects, and to a N-demethyl metabolite with a less clear function.

Elimination

Excretion is mainly in the faeces (50%) but also via the kidneys (less than 4% as unchanged drug, about 30% as metabolites). The plasma elimination half-life is approx. 10 hours.

PRECLINICAL SAFETY DATA

In embryotoxicity studies in rats and rabbits, thioridazine proved to be non-teratogenic.

A 52-week toxicity study in rats and a 6-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.

EXCIPIENTS

Film-coated tablets: Colloidal silica, hydroxypropylmethylcellulose, indigo carmine lake (Indigotin lake*), lactose, magnesium stearate, maize starch, polyvinylpyrrolidone, talc, titanium dioxide, yellow iron oxide (E 172).

*) Brown iron oxide instead of indigo carmine lake in 25mg tablets.

Prolonged-release tablets: Cellulose acetate phthalate, cellulose microcrystalline, cetylalcohol, dimethylsilicone oil, magnesium stearate, polyvinyl acetate, yellow iron oxide (E 172), red iron oxide (E 172).

Oral drops, solution: Ethanol, flavouring agent, methylhydroxybenzoate, propylhydroxybenzoate, sorbitol, purified water.

Oral suspension (0.5%): Flavouring agent, polyacrylic acid, polysorbate, sodium hydroxide, sucrose, purified water.

Pharmaceutical formulations may vary between countries.

INCOMPATIBILITIES

Not applicable.

STORAGE

Melleril oral solution turns blue when left standing in the light. This colour change is reversible in the dark and has no influence on the activity or tolerability of the product.

Dilution of Melleril oral solution in water may result in turbidity due to fine precipitation of the active ingredient. Although the efficacy and tolerability of the product are not influenced by this turbidity, the solution should be taken immediately after dilution.

The oral suspension and the oral drops, solution should be protected from heat (do not store above 25°C).

Melleril film-coated tablets, prolonged-release tablets and oral drops, solution should be protected from light. Keep the container in the outer carton.

MELLERIL[®] should not be used after the date marked "EXP" on the pack.

INSTRUCTIONS FOR USE AND HANDLING

Tablets

Swallow the tablet with a full glass of water. Do not chew Melleril prolonged-release tablets.

Liquid forms

Add the dose of liquid Melleril to a glass of water or fruit juice just before you drink it.

Melleril oral solution may turn blue if left standing in the light or may produce a cloudy solution when added to water. These changes will not affect the way in which Melleril works or cause any unwanted effects.

Note: MELLERIL[®] should be kept out of the reach and sight of children.

Manufacturer:

See folding box.

® = registered trademark

International Package Leaflet

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Novartis Pharma AG, Basel, Switzerland