

PRODUCT MONOGRAPH

^{Pr} Majeptil *

Thiopropazine Mesylate Tablets

10mg Thiopropazine (as Thiopropazine Mesylate)

Neuroleptic

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Pr Majeptil®

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Thioproperazine Mesylate Tablets

Neuroleptic

ACTION

Thioproperazine is a potent neuroleptic with antipsychotic properties.

Thioproperazine has a marked cataleptic and antiapomorphine activity associated with relatively slight sedative, hypothermic and spasmolytic effects. It is virtually without antiserotonin and hypotensive action and has no antihistaminic property.

INDICATIONS

All types of acute and chronic schizophrenia, including those which did not respond to the usual neuroleptics; manic syndromes.

CONTRAINDICATIONS

Comatose or depressive states including those induced by CNS depressants; Parkinson's disease; blood dyscrasias; in patients with spastic diseases and in senile patients with pre-existing Parkinson-like symptoms; in children under 3 years of age and in patients generally sensitive to phenothiazines.

WARNINGS

Treatment should be discontinued if a severe neurologic syndrome is observed, especially when hypertonia is accompanied by dysphagia and/or marked autonomic disturbances.

Neuroleptic phenothiazines may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e. drug induced) QT prolongation. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment. (See also **ADVERSE REACTIONS**).

Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstated, when the dosage is increased or when a switch is made to a different antipsychotic drug. Thioproperazine should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. The lowest effective dose and the shortest duration of treatment should be used, and

treatment should be discontinued at the earliest opportunity, or if a satisfactory response cannot be obtained. If the signs and symptoms of tardive dyskinesia appear during treatment, discontinuation of thioproperazine should be considered.

Neuroleptic Malignant Syndrome (NMS): NMS may occur in patients receiving antipsychotic drugs. NMS is characterized by hyperthermia, muscle rigidity, altered consciousness and signs of autonomic instability including irregular blood pressure, tachycardia, cardiac arrhythmias and diaphoresis. Additional signs may include elevated serum creatinine kinase, myoglobinuria (rhabdomyolysis), acute renal failure and leukocytosis. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Risk of Stroke: In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patients cannot be excluded. MAJEPTIL should be used with caution in patients with stroke risk factors.

Elderly Patients with Dementia: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Hematologic:

Venous Thromboembolism

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

Pregnant Women:

The safety of thioproperazine in pregnant women has not been clearly established, therefore it should not be used during the first trimester of pregnancy.

Non-teratogenic effects: Neonates exposed to antipsychotic drugs including MAJEPTIL 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, various degrees of respiratory disorders ranging from tachypnoea to respiratory distress and bradycardia. Although these events occurred most often when other drugs such as psychotropic or antimuscarinic drugs were coadministered, they may also occur with antipsychotic use alone. Signs related to atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, abdominal bloating, tachycardia and feeding disorder in neonates can also occur. 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. Appropriate monitoring and treatment of neonates born to mothers receiving MAJEPTIL are recommended

Since the safety of MAJEPTIL during pregnancy has not been established, MAJEPTIL should not be used during pregnancy or in women of child bearing potential unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

Occupational Hazards: Because drowsiness, slowing of reaction time or impaired judgment may occur, patients should generally not operate a motor vehicle or engage in dangerous activities while under the action of the drug.

PRECAUTIONS

Before starting treatment with thioproperazine, it is recommended to ascertain that the cardiovascular system and the liver and kidney functions are unimpaired.

Treatment should be initiated by the oral route with a low initial dosage, increased progressively.

Since thioproperazine may potentiate the action of general anesthetics, morphine-like analgesics, barbiturates, alcohol, and other CNS depressants, care should be exercised when these agents are given with it.

The antiemetic effect of thioproperazine may obscure symptoms such as vomiting and nausea, normally associated with some types of organic disease (intestinal obstruction and brain tumor).

Thioproperazine should be used cautiously in patients with a history of seizures.

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

Hyperglycemia: Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Hyperglycemia or intolerance to glucose has been reported in patients treated with MAJEPTIL. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on MAJEPTIL should get appropriate glycaemic monitoring during treatment.

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

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

ADVERSE REACTIONS

Neuromuscular (extrapyramidal) reactions are the most frequently observed. They are usually dose-related and generally subside when the dose is reduced or when the drug is temporarily discontinued. Administration of an antiparkinsonian agent is usually, but not always, effective in reversing the neuromuscular reactions associated with this and other phenothiazines.

Anxiety or apathy, elation or depression, drowsiness and/or insomnia are not infrequently observed.

Occasional disturbances of accommodation, rare cases of headache and exceptionally, cases of nausea and vomiting, constipation or diarrhea have been reported. Lacrimation, sialorrhea and profuse sweating are more frequent. Oliguria may occur.

Very rare cases of QT interval prolongation have been reported with other neuroleptics. There have been isolated reports of sudden death, with possible causes of cardiac origin (see **WARNINGS**), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

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

Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs (see also **WARNINGS**).

Intolerance to glucose, hyperglycemia have been reported (see **PRECAUTIONS**).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Symptoms: Overdosage may result in severe extrapyramidal symptoms with dysphagia, marked sialorrhea, persistent and rapidly increasing hyperthermia, pulmonary syndrome, state of shock with pallor and profuse sweating, which may be followed by collapse and coma.

Treatment: There is no specific antidote. When mild symptoms are present (e.g., in regular therapy) corrective measures are usually sufficient:
Administration of thioproperazine should be discontinued.

Against Dyskinetic Manifestations: An antiparkinsonian or chloral hydrate, but the latter should be used with caution, as it may further depress the respiration.

In the presence of severe symptoms (e.g., in cases of overdose) in addition to the above corrective measures, the following supportive treatment should be carried out:

Gastric Lavage: Because of the antiemetic effect of thioproperazine, centrally acting emetics will remain ineffective.

In cases of severe hypotension or collapse: norepinephrine and adrenocortical hormones to restore blood pressure. Since phenothiazines are known to reverse the pressor action of epinephrine, the latter should not be used as it may further lower blood pressure.

Against Respiratory Depression: oxygen inhalation and, if necessary, tracheal intubation.

Against Dehydration: i.v. infusion of dextrose in normal saline.

Against Respiratory Infection: broad spectrum antibiotics.

DOSAGE AND ADMINISTRATION

Initial Treatment: Adults: It is recommended to start treatment at a low dosage of about 5 mg per day in a single dose or in divided doses. This initial dosage is gradually increased by the same amount every 2 to 3 days until the usual effective dosage of 30 to 40 mg per day is reached. In some cases higher dosages of 90 mg or more per day, are necessary to control the psychotic manifestations.

Children: In children over 10 years: Start treatment with a daily dosage of 1 to 3 mg following the method of treatment described for adults.

Maintenance Therapy: Adults and Children: Dosage should be reduced gradually to the lowest effective level, which may be as low as a few mg per day and maintained as long as necessary.

Other Method of Treatment: Occasionally, thioproperazine is prescribed in the form of discontinuous treatment at 5 or 10 mg, 3 times a day, until the onset of severe extrapyramidal symptoms. Then, treatment is discontinued until spontaneous full recovery from these symptoms. The same course of therapy is repeated for at least 3 consecutive treatments. Discontinuous treatment should be reserved for resistant cases, and performed in hospitalized patients, under close medical supervision.

AVAILABILITY OF DOSAGE FORMS

Each cylindrical biconvex, predominantly orange tablets with possible mottled aspect contains: thioproperazine base (as the mesylate) 10 mg. Nonmedicinal ingredients: acetic anhydride, calcium phosphate, carnauba wax, cellulose, colloidal silicon dioxide, diethyl phthalate, FD&C Yellow No 6 aluminum lake, magnesium stearate, polacrillin potassium, sodium oleate, titanium oxide and zein. Tartrazine-free. Bottles of 100.

Storage condition: Protect from light. Store between 15 – 30 °C.

PART III: CONSUMER INFORMATION

Pr Majeptil
Thiopropazine mesylate tablets

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

ABOUT THIS MEDICATION

What the medication is used for:

MAJEPTIL is a medication used to treat all types of acute and chronic schizophrenia, including those which did not respond to the usual antischizophrenic medication. It is also used to treat manic episodes.

What it does:

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

When it should not be used:

You should not use Majeptil if you have:

- An allergy to thiopropazine mesylate, to any of its ingredients or to phenothiazines
- A medical condition known as pheochromocytoma (a tumor of the adrenal gland)
- A severe heart or blood vessel disorder
- Severe kidney problems
- Had brain damage
- Liver disease
- A blood cell disorder such as anemia, low white blood cell counts, or low platelets
- Drowsiness, slow breathing, weak pulse
- Decreased alertness caused by taking certain medications or drinking alcohol
- You are going to receive anesthesia in the spine or for a region (such as an arm, leg or the lower part of your body)
- Parkinson's Disease
- If you are under three years old

What the medicinal ingredient is:

Thiopropazine mesylate

What the nonmedicinal ingredients are:

Acetic anhydride, calcium phosphate, carnauba wax, cellulose, colloidal silicon dioxide, diethyl phthalate, FD&C Yellow No 6 aluminum lake, magnesium stearate, polacrillin potassium, sodium oleate, titanium oxide and zein.

What dosage forms it comes in:

Tablet, 10 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

BEFORE you use Majeptil talk to your doctor or pharmacist if:

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

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

Effects on Newborns:

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

People who take Majeptil are cautioned:

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

INTERACTIONS WITH THIS MEDICATION

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

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

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

Drugs that may interact with Majepzil include: anti-anxiety agents, antidepressants, muscle relaxants, anti-seizure medicine, high blood pressure medicine, cabergoline, metrizamide, guanethidine, guanadrel, grepafloxacin, sparfloxacin, lithium, cisapride, atropine-like drugs, narcotic pain relievers (e.g., codeine), drugs used to aid sleep, drowsiness-causing antihistamines (e.g., diphenhydramine), other drugs that may make you drowsy, general anesthetics.

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

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

PROPER USE OF THIS MEDICATION

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

Your doctor will decide which dose is best for you.

Usual dose:

Adults:

Usual Initial dose: 5 mg a day in a single dose or divided doses.

Usual Optimal Dose: 30 to 40 mg per day.

This usual optimal dose can be increased by your physician.

Maintenance Dose: Your doctor will decrease your dose to the lowest effective level. Always follow the doctor's instructions.

Children (Over 10 years Old):

Usual Initial dose: 1 to 3 mg a day in a single dose or divided doses.

The physician will determine the best dosage for your child. Always follow the doctor's instructions.

Overdose:

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

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

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Side effects may include: anxiety, lack of feeling or emotion, depression, difficulty sleeping, cramps, diarrhea or constipation, sweating, reduced amount of urine, urinary incontinence, dizziness, drowsiness, dry mouth or drooling, nasal congestion, nausea and vomiting, headache, menstrual changes, change in libido, swelling of the breasts and milk production in both men and women, weight changes, teary eyes and blurred vision.

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

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

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

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

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Unknown	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Neuroleptic Malignant Syndrome: any group of symptoms which may include high fever, sweating, stiff muscles, fast heartbeat, fast breathing and feeling confused, drowsy or agitated			✓
	Extrapyramidal Symptoms: muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want.			✓
	Fast or irregular heartbeat		✓	
	Seizures or fits			✓
	Long-lasting (greater than 4 hours in duration) and painful erection of penis			✓

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
	Only if severe	In all cases	
Tardive Dyskinesia: uncontrollable movements or twitches of the body, face, eyes or tongue, stretching the neck and body		✓	
Low Blood Pressure: feeling of Lightheadedness or fainting especially when getting up from a lying or sitting position		✓	
High Blood Pressure: headaches, vision disorders, nausea and vomiting		✓	
Decreased sweating		✓	
Jaundice: yellow colour to skin and eyes, dark urine		✓	
Respiratory Infection: fever, flu-like symptoms, coughing, difficult or fast breathing		✓	
New or worsening constipation		✓	
Akathisia: a feeling of restlessness, inability to remain motionless		✓	
Vision Changes: blurred vision, glaucoma or other eye disorder		✓	
Increased Blood Sugar: frequent urination, thirst and hunger	✓		

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Uncommon	Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.		✓	

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
<http://www.searchlightpharma.com>
 or by contacting the sponsor, Searchlight Pharma Inc., at:
 1-647-945-9762

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HOW TO STORE IT

Store this medication at room temperature between 15 and 30 °C away from heat and light. Do not store in the bathroom. Keep this and all medications out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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