PRESCRIBING INFORMATION

TRIFLUOPERAZINE

Trifluoperazine Hydrochloride Tablets BP

1, 2, 5, 10 and 20 mg

Antianxiety-Antiemetic-Antipsychotic

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TRIFLUOPERAZINE
(Trifluoperazine Hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
oral	Tablets:1 mg, 2 mg, 5 mg, 10 mg and 20 mg	carnauba wax, cornstarch, FD&C Blue #2 aluminum lake, hydroxypropyl methyl-cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

INDICATIONS AND CLINICAL USE

TRIFLUOPERAZINE is indicated for:

- Control of excessive anxiety, tension and agitation seen in neuroses or associated with somatic conditions.
- Treatment or prevention of nausea and vomiting of various causes.
- Management of psychotic disorders, such as acute or chronic catatonic, hebephrenic and paranoid schizophrenia; psychosis due to organic brain damage, toxic psychosis, and the manic phase of manic-depressive illness.

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

Pediatrics (under 6 years of age):
The safety and efficacy of TRIFLUOPERAZINE in children under the age of 6 have not been studied (see Special Populations)

CONTRAINDICATIONS

TRIFLUOPERAZINE is contraindicated in:

- Patients who are hypersensitive to this drug, to phenothiazines or to any ingredient in the formulation. (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Comatose or greatly depressed states due to CNS depressants.
- Blood dyscrasias and bone marrow depression
- Liver damage
- Patients with congenital long QT syndrome or with a family history of this syndrome and in patients with a history of cardiac arrhythmias or Torsade de Pointes. A pre-treatment ECG is thus recommended to exclude these conditions. Trifluoperazine should not be used in the case of acquired long QT interval, such as associated with concomitant use of drugs known to prolong the QT interval (see DRUG INTERACTIONS), known hypokalemia or hypomagnesemia, or clinically significant bradycardia.
- Combination with serotonin reuptake inhibitors, such as citalopram **(**see DRUG INTERACTIONS).

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

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

General

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

Cardiovascular

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

Phenothiazines can produce alpha-adrenergic blockade. Because hypotension has occurred, large doses should be avoided in patients with impaired cardiovascular systems. To further minimize the occurrence of hypotension after initial administration, keep patient lying down and observe for at least 0.5 hour. If hypotension occurs, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine or phenylephrine is suitable. Other pressor agents, including epinephrine, should not be used as they may cause a paradoxical further lowering of blood pressure, (see SYMPTOMS AND TREATMENT OF OVERDOSE)

Trifluoperazine therapy may produce an increase in mental and physical activity. In certain instances, this effect may not be desirable. For example, some patients with angina pectoris have complained of increased pain while taking trifluoperazine; therefore, if trifluoperazine is used in angina patients, such patients should be observed carefully and if an unfavorable response is noted, the drug should be withdrawn.

Prolongation of QT Interval
Use with caution in patients with cardiovascular disease or family history of QT prolongation. Avoid concomitant QT prolonging drugs. Caution should be used in patients with cardiovascular disease or family history of QT prolongation.

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

- female
- age 65 years or older
- baseline prolongation of the QT/QTc interval
- presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes
- family history of QT prolongation, or sudden cardiac death at <50 years
- cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left

ventricular hypertrophy, cardiomyopathy, conduction system disease)
- history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation)
- electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- bradycardia
- acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma)
- hepatic dysfunction, renal dysfunction, and/or phenotypic/genotypic poor metabolizers of drug metabolizing enzyme isoforms, if relevant to the elimination of the drug.
- diabetes mellitus
- nutritional deficit
- autonomic neuropathy

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

Endocrine and Metabolism

Hormonal effects of antipsychotic/neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynecomastia, oligomenorrhea or amenorrhoea, and erectile dysfunction. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

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 neuroleptic drugs is contemplated in a patient with a previously detected breast cancer. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. The clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies, nor epidemiological studies conducted to date, have shown an association between chronic administration of these drugs and mammary tumorogenesis; the available evidence is considered too limited to be conclusive at this time.

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

Gastrointestinal

The antiemetic action of trifluoperazine may mask signs and symptoms of toxicity or overdosage of other drugs or may obscure the diagnosis of conditions such as intestinal obstruction, brain tumor and Reye's syndrome.

Genitourinary

Rare cases of priapism have been reported with antipsychotics drug. This adverse reaction, as

with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

Rare cases of blood dyscrasias (agranulocytosis, anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia) and jaundice of the cholestatic type have been reported in patients receiving high doses of trifluoperazine. Therefore, the physician should bear in mind the possibility of such reactions and hematological monitoring is recommended.

Patients who have experienced blood dyscrasias or bone marrow suppression with a phenothiazine should not be re-exposed to any phenothiazine, including Trifluoperazine unless in the judgement of the doctor the potential benefits of treatment outweigh the possible hazards.

Venous thromboembolism (VTE)

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

Hepatic/Biliary/Pancreatic

Jaundice of the cholestatic type of hepatitis or liver damage has been reported. Patients who have experienced jaundice with a phenothiazine should not be re-exposed to any phenothiazine, including trifluoperazine, unless in the judgement of the doctor the potential benefits of treatment outweigh the possible hazards. Hepatic and renal function should be checked

Neurologic

Neuroleptic Malignant Syndrome (NMS)

Patients treated with Trifluoperazine can develop neuroleptic malignant syndrome: an idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability (irregular pulse or blood pressure, diaphoresis), and altered consciousness. Patients with Parkinson's disease or dementia may be at increased risk. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

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

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

Anticonvulsants: Since Trifluoperazine may lower the convulsive threshold, it should be used with caution in patients with epilepsy, EEG abnormalities or subcortical brain damage. Dosage adjustment of anti-convulsant may be necessary.

Effects on Driving Ability and Use of Machinery:
Trifluoperazine may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, patients should be cautioned about activities requiring alertness (e.g., operating vehicles or machinery).

Dependence/Tolerance

Although phenothiazines cause neither psychic nor physical dependence, sudden discontinuance in long-term psychiatric patients may cause temporary symptoms, e.g., nausea and vomiting, dizziness, tremulousness.

Carcinogenesis and Mutagenesis
Phenothiazines have been found to be mutagenic with in vivo administration to rodents and in vitro administration to human cells and bacteria. No clinical relevance has been established.

Ophthalmologic
As with all drugs which exert an anticholinergic effect or cause mydriasis, trifluoperazine should be used with caution in patients with glaucoma.

Phenothiazines have been reported to produce retinopathy, especially with long-term treatment at high dosage. Should ophthalmoscopic examination or visual field studies demonstrate retinal changes in patients on trifluoperazine, the drug should be discontinued.

Skin
Skin pigmentation have been reported in a few hospitalized mental patients taking substantial doses of some phenothiazine derivatives for prolonged periods. Present evidence suggests that these changes may be reversible.

Long-Term Therapy
With prolonged administration at high dosages, the possibility of cumulative effects, with sudden onset of severe CNS or vasomotor symptoms, should be kept in mind. To lessen the likelihood of adverse reactions related to cumulative drug effect, patients with a history of long-term therapy with trifluoperazine HCl and/or other antipsychotics should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

Patients on long-term phenothiazine therapy require regular and careful surveillance with particular attention to tardive dyskinesia and possible eye changes, blood dyscrasias, liver dysfunction and myocardial conduction defects, particularly if other concurrently administered drugs have potential effects in these systems.

Although phenothiazines cause neither psychic nor physical dependence, sudden discontinuance

in long-term psychiatric patients may cause temporary symptoms, e.g., nausea and vomiting, dizziness, tremulousness.

Special Populations

Pregnant Women:
Safety for the use of Trifluoperazine during pregnancy has not been established.
When given in high doses during late pregnancy, phenothiazines have caused prolonged extrapyramidal disturbances in the child. There are also reports of prolonged jaundice and hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

Animal reproduction studies and follow-up studies in 819 women in Canada and Great Britain, who had taken trifluoperazine during pregnancy, showed no causal relationship between the drug and congenital malformations. Nonetheless, it should not be administered to pregnant women, particularly during the first trimester of pregnancy, unless, in the opinion of the physician, the expected benefits of the drug to the patient outweigh the potential risk to the fetus or child.

Nursing Women:
There is evidence that phenothiazines are excreted in the milk of nursing mothers.

Pediatrics (under 6 years of age):
The safety and efficacy of Trifluoperazine in children under the age of 6 have not been studied.

Geriatrics (≥65 years of age):
The safety and efficacy of Trifluoperazine in patients 65 years of age or older have not been studied. Caution should be exercised with the use of Trifluoperazine in the elderly patient, recognizing the more frequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication in this population. (see DOSAGE AND ADMINISTRATION).

Use in Geriatric Patients with Dementia
Care should be exercised in treating elderly or debilitated patients as some appear prone to neurological adverse reactions.

Monitoring and Laboratory Tests

Phenothiazines may result in falsely positive or negative pregnancy test results due to interference based on immunological reactions between human chorionic gonadotropin (HCG) and anti-HCG.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects with different phenothiazines vary in type, frequency, and mechanism of

occurrence, i.e., some are dose-related, while others involve individual patient sensitivity. Some adverse effects may be more likely to occur in patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines

At therapeutic dosage levels, adverse reactions are infrequent, usually mild and transient; and unlikely to affect the course of treatment. Drowsiness, dizziness, skin reactions, dry mouth, stimulation, insomnia, fatigue, weakness, anorexia, amenorrhea, lactation and blurred vision may be seen occasionally. Extrapyramidal symptoms may occur but are rare at dosages of 6 mg or less. Tardive dyskinesia has been reported.

Trifluoperazine may impair mental and/or physical abilities, especially during the first few days of therapy. Patients should be cautioned about activities requiring alertness, e.g. driving a car or operating machinery.

Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. (See WARNINGS and PRECAUTIONS)

Extrapyramidal Symptoms

These symptoms are seen in a significant number of hospitalized mental patients receiving higher dosages of trifluoperazine (10 mg to 40 mg or more daily). They may be characterized by motor restlessness, may be of the dystonic type, or may resemble parkinsonism. Depending on the severity of symptoms, dosage should be reduced or discontinued. If therapy is reinstituted, it should be a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstated. Administration of an antiparkinsonism agent (except levodopa) can be considered for severe cases. Suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed.

Motor Restlessness

Symptoms may include agitation or jitteriness and sometimes insomnia. These symptoms often disappear spontaneously. At times these symptoms may be similar to the original neurotic or psychotic symptoms. Dosage should not be increased until these side effects have subsided.

Dystonias

Symptoms may include spasm of the neck muscles, sometimes progressing to torticollis; extensor rigidity of back muscles; sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crises and protrusion of the tongue. The onset of the dystonias may be sudden. They may last several minutes, disappear and then recur. Prodromic symptoms are usually present. There is typically no loss of consciousness.

They usually subside within a few hours, and almost always within 24 to 48 hours after the drug has been discontinued. In mild cases, reassurance is often sufficient. In more severe adult cases, the administration of an antiparkinsonism agent, except levodopa, usually improve symptoms. In children, reassurance will usually control symptoms.

Neuroleptic Malignant Syndrome

As with other neuroleptic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated CPK, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal and requires symptomatic treatment and immediate discontinuation of neuroleptic treatment.

Pseudoparkinsonism

Symptoms may include mask-like facies, drooling, tremor, pillrolling motion, cogwheel rigidity and shuffling gait. Reassurance and sedation are important. In most cases these symptoms are reversible when an antiparkinsonism agent is administered concomitantly. (Note: Antiparkinsonism agents should be used only when required. Levodopa has not been found effective in pseudoparkinsonism.) Occasionally it is necessary to lower the dosage or discontinue the drug temporarily.

Tardive Dyskinesia

This syndrome may occur in some patients on long-term therapy with phenothiazines, including trifluoperazine, or may appear after drug treatment has been discontinued. The risk appears to be greater in elderly patients, especially females, on high-dose therapy. The syndrome is characterized by rhythmical involuntary movements of the tongue and facial muscles (e.g., protrusion of the tongue, puffing of cheeks, puckering of mouth, chewing movements) and sometimes of the extremities. The symptoms may persist for many months or even years, and while they gradually disappear in some patients, they appear to be irreversible in others.

There is no known effective treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. If there is a reinstitution of treatment, or an increase in the dosage of the drug, or a switch to a different antipsychotic agent, the syndrome may be masked. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop.

Cardiovascular

ECG changes, particularly nonspecific, usually reversible Q and T wave distortions, have been observed in some patients receiving phenothiazine tranquilizers. This relationship to myocardial damage has not been confirmed.

Other ECG changes can include non-specific transient Q and T wave abnormalities, QT Prolongation, hypotension, cardiac arrhythmias including atrioventricular block, paroxysmal tachycardia, ventricular fibrillation and cardiac arrest, Ventricular arrhythmias, and Torsades de pointes.

Haematological

Blood dyscrasias including pancytopenia, agranulocytosis, thrombocytopenic purpura, leucopoenia, eosinophilia, haemolytic anaemia, aplastic anaemia (see WARNINGS and PRECAUTIONS).

Other Adverse Reactions

Not all of the following adverse effects have been seen with every phenothiazine, however they have been reported with use of this drug class.

Central nervous system: drowsiness, dizziness, fatigue, blurred vision, seizures (particularly in patients with EEG abnormalities), altered CSF proteins, cerebral oedema, prolongation of the action of CNS depressants (opiates, alcohol, barbiturates), autonomic reactions (mouth dryness nasal congestion, headache, nausea, constipation, ileus, impotence, urinary retention, priapism, miosis, and mydriasis), muscular weakness, reactivation of psychotic processes (catatonic-like states), increased aggressiveness, and toxic confusional states.

DRUG INTERACTIONS

Overview

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant administration of propranolol with phenothiazines results in increased plasma levels of both drugs.

Phenothiazines may lower the convulsive threshold; dosage adjustment of anticonvulsants may be necessary. Potentiation of anticonvulsant effects does not occur. However, it has been reported that phenothiazines may interfere with the metabolism of phenytoin and thus precipitate phenytoin toxicity.

Drugs that lower the seizure threshold, including phenothiazine derivatives, should not be used with metrizamide. Trifluoperazine should be discontinued at least 48 hours before myelography, should not be resumed for at least 24 hours post procedure, and should not be used for the control of nausea and vomiting occurring either prior to myelography or post procedure.

If agents such as sedatives, narcotics, anesthetics, tranquilizers or alcohol are used either simultaneously or successively with trifluoperazine, the possibility of an undesirable additive depressant effect should be considered.

Antihypertensives

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

Levodopa Trifluoperazine may, in a dose-related way, impair the antiparkinson effect of

levodopa.

CNS
Phenothiazines may potentiate the effect of atropine and organophosphate insecticides.

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

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

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide)
- antipsychotics (e.g., chlorpromazine, pimozide, droperidol)
- antidepressants (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants)
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin)
- quinolone antibiotics (e.g., moxifloxacin)
- pentamidine
- antimalarials (e.g., quinine)
- azole antifungals (e.g., fluconazole, itraconazole**,** ketoconazole, ,voriconazole)
- domperidone
- tacrolimus
- 5-HT3 antagonists (e.g., dolasetron, ondansetron)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

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

Do not administer in combination with drugs causing electrolyte alteration. Concomitant use with diuretics should be avoided, in particular those causing hypokalemia.

SSRI (Selective Serotonin Reuptake Inhibitor) Antidepressants
Combination with serotonin reuptake inhibitors, such as citalopram may result in an increased risk of QT interval prolongation.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

Trifluoperazine dosage must be adjusted to the severity of the symptoms under treatment, and to the response of the individual. Particularly in psychiatric patients, dosage should be titrated carefully in order to achieve maximum therapeutic effect with the lowest possible dose, thereby minimizing the occurrence of unwanted side effects.

Debilitated patients: usually require a lower initial dose and more gradual dosage titration than do younger and healthier patients

Geriatrics: usually require a lower initial dose and more gradual dosage titration than do younger and healthier patients

Liver disease: trifluoperazine is metabolized in the liver, dose reductions should be considered in patients with hepatic dysfunction.

Recommended Dose and Dosage Adjustment

Adults:

Mild to moderate symptoms:

Usual dosage is 1 or 2 mg twice daily. If necessary, dosage may be increased to 6 mg daily but above this level extrapyramidal symptoms are more likely to occur in some patients.

Moderate to severe symptoms:

The usual starting dose is 5 mg administered orally 2 or 3 times daily. Dosage should be increased gradually. The majority of patients will show optimum response on 15 to 20 mg/day, although a few may require 40 mg or more. Some patients have been given 80 mg or more daily, but there is now every evidence that such high dosages are rarely necessary. Optimum dosage levels are usually reached within 2 or 3 weeks after the start of therapy. It is important to maintain therapeutic dosage levels for a sufficient time to produce maximum improvement. In most hospitalized acute cases, 2 to 3 weeks at optimum dosage will suffice before gradual reduction to maintenance dosage levels is begun.

Children: (6 to 12 years of age)

Behavior Disorders in Children:
The usual dose is a 1 mg administered once or twice a day, depending on the child bodyweight. (see also below: Dosage, Psychotic children).

Psychotic Children: (either hospitalized or under adequate supervision.)
The usual starting dose is a 1 mg administered once or twice daily, depending on the child bodyweight. Dosage may be gradually increased until symptoms are controlled or until side effects become troublesome. Both the rate and the amount of dosage increases should be carefully adjusted to the weight and the severity of the symptoms, and the lowest effective dosage should always be used. Once control is achieved, it is usually possible to reduce dosage to a satisfactory maintenance level. In most cases, it is not necessary to exceed 15 mg of trifluoperazine daily. .

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

OVERDOSAGE

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

Symptoms:
Signs and symptoms will be predominantly extrapyramidal. Lesser degrees of overdosage may cause muscular twitching, drowsiness or dizziness. Symptoms of gross overdosage may include CNS depression, weakness, tremor, torticollis and dystonia. Agitation and restlessness may occur. Salivation, dysphagia, or disturbances of gait may also be present. Hypotension may occur.

Treatment:
Treatment is essentially symptomatic and supportive. Gastric lavage is helpful if performed early. **Do not attempt to induce emesis because a dystonic reaction of the head or neck may develop that could result in aspiration of vomitus.**

The patient should be kept under careful observation and particular attention should be directed to maintaining an open airway, since involvement of the extrapyramidal mechanism may produce dysphagia and respiratory difficulty in severe cases of overdosage.

If hypotension occurs, the standard measures for managing circulatory shock should be initiated. If it is desirable to administer a vasoconstrictor, norepinephrine or phenylephrine is most suitable. Other pressor agents, including epinephrine, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents and cause a further lowering of blood pressure.

Extrapyramidal symptoms may be treated with antiparkinsonism drugs (**except levodopa**) or

diphenhydramine.

Limited experience indicates that phenothiazines are not dialyzable.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mode of action of the phenothiazines has not yet been definitely established. Existing information suggests the following possibilities:

Antipsychotic/antianxiety effects: Observations suggest that the primary action is to depress the physiologic accompaniments of the emotional factors of the personality which are believed to be basically evoked by the limbic system and its connections with the hypothalamus.

Experimental and clinical evidence indicates that the phenothiazines act on the subcortical areas of the CNS which influence the affective functions. Trifluoperazine is more specific than other phenothiazines in its activity. Its effects seem limited to parts of the basal ganglia, such as the amygdaloid nucleus.

The fact that trifluoperazine modifies behavior of opposite extremes toward more normal activity suggests that the drug is not working on behavior per se but on some factor or factors underlying behavior. Its rapidity of action, increased potency and effectiveness in chronic regressed patients in whom other agents were less effective are believed due to its specificity of action.

Antiemetic effect:
The phenothiazines (including trifluoperazine) inhibit indirect stimulation of the vomiting centre, but do not inhibit indirect stimulation of the centre by gastrointestinal stimulants. Because of this, it is believed that their site of action is the chemoreceptor trigger zone.

Onset of action occurs normally within 0.5 to 1 hour following tablet administration. Onset is slightly more rapid with the concentrate form because no disintegration time is involved. Onset usually occurs within 10 to 15 minutes when trifluoperazine is administered i.m., and within 5 to 15 minutes following i.v. administration. Peak activity occurs within 2 hours in animals. Clinical observations indicate that disappearance of, or marked reduction in psychomotor activity and hallucinations, occurs within hours after i.m. administration of trifluoperazine.

STORAGE AND STABILITY

Store at controlled room temperature (15°C-30°C) in well-closed containers. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TRIFLUOPERAZINE 1 mg**:** Each deep blue, round, biconvex, film-coated tablet, engraved 1 on one side contains trifluoperazine hydrochloride equivalent to 1 mg trifluoperazine. Available in bottles of 100 and 1000, and in unit dose packages of 100 (10 X10) tablets.

TRIFLUOPERAZINE 2 mg**:** Each deep blue, round, biconvex, film-coated tablet, engraved 2 on one side contains trifluoperazine hydrochloride equivalent to 2 mg trifluoperazine. Available in bottles of 100 and 1000, and in unit dose packages of 100 (10 X10) tablets.

TRIFLUOPERAZINE 5 mg**:** Each deep blue, round, biconvex, film-coated tablet, engraved 5 on one side contains trifluoperazine hydrochloride equivalent to 5 mg trifluoperazine. Available in bottles of 100 and 1000, and in unit dose packages of 100 (10 X10) tablets.

TRIFLUOPERAZINE 10 mg: Each deep blue, round, biconvex, film-coated tablet, engraved 10 on one side contains trifluoperazine hydrochloride equivalent to 10 mg trifluoperazine. Available in bottles of 100 and 1000 tablets.

TRIFLUOPERAZINE 20 mg: Each deep blue, round, biconvex, film-coated tablet, engraved 20 on one side contains trifluoperazine hydrochloride equivalent to 20 mg trifluoperazine. Available in bottles of 100.

In addition to the active ingredient, trifluoperazine hydrochloride, each tablets also contains the non-medicinal ingredients; carnauba wax, cornstarch, FD&C Blue #2 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

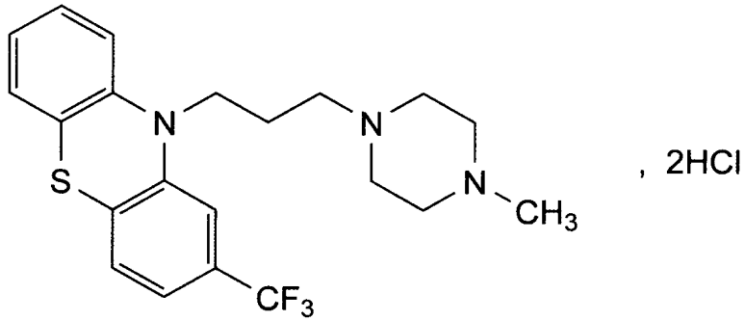
Drug Substance

Proper name: Trifluoperazine Hydrochloride BP

Chemical name: 10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)-10*H*-phenothiazine

Molecular formula and molecular mass: $C_{21}H_{24}F_3N_3S$, 2HCl 480.4

Structural formula:



Physicochemical properties:

Melting Range: ~ 242 °C, with decomposition.

Description: White to pale yellow, crystalline powder.

PART III: CONSUMER INFORMATION

TRIFLUOPERAZINE
Trifluoperazine Hydrochloride Tablets BP

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

ABOUT THIS MEDICATION

What the medication is used for:
• Trifluoperazine is used to control the symptoms of anxiety, tension and agitation seen in neuroses or associated with somatic conditions.
• Trifluoperazine may also be used to treat nausea and vomiting..
• Trifluoperazine is also used in the management of catatonia, schizophrenia; various types of psychosis, and the manic phase of manic-depressive illness.

What it does:

Trifluoperazine 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 Trifluoperazine works is unknown. However, it seems to readjust the balance of dopamine and serotonin.

When it should not be used:
You should not use Trifluoperazine if you:
- Have an allergy to trifluoperazine, to any of its nonmedicinal ingredients or to phenothiazines.
- Have a medical condition called as pheochromocytoma (a tumor of the adrenal gland)
- Have a severe heart or blood vessel disorder
- Have severe kidney problems
- Have liver disease
- Have a blood cell disorder such as anemia, low white blood cell counts, or low platelets
- Have drowsiness, slow breathing, weak pulse
- Have decreased alertness caused by taking certain medications or drinking alcohol
- Are going to receive anesthesia in the spine or for a region (such as an arm, leg or the lower part of your body)
- Are going to have a special X-ray examination of the brain or spinal cord involving a chemical called metrizamide (your doctor will be able to help you).

What the medicinal ingredient is:
Trifluoperazine hydrochloride

What the nonmedicinal ingredients are:
carnauba wax, cornstarch, FD&C Blue #2 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide**.**

What dosage forms it comes in:
1 mg, 2 mg, 5 mg, 10 mg and 20 mg tablets

WARNINGS AND PRECAUTIONS

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

BEFORE you use TRIFLUOPERAZINE talk to your doctor or pharmacist if:
- You have heart disease, irregular heart beats, glaucoma or prostatic hypertrophy
- You have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reason, or take oral contraceptives ("The Pill").
- you have had a stroke or you have uncontrolled high blood pressure, diabetes, high cholesterol or a family history of strokes.
- You are taking barbiturates, painkillers, narcotics, antihistamines or other drugs that make you drowsy
- You are drinking alcohol every day. You should not take Trifluoperazine if you are under the effects of alcohol.
- You suffer from a brain disorder causing tremors, rigidity and slowing of movement (Parkinson's disease).
- You have a debilitating condition, including dementia.
- You have or ever had a blackout or seizure
- You are pregnant. Trifluoperazine should not be used during pregnancy unless your doctor considers the benefits to you markedly outweigh the potential risks to the fetus
- You are breast feeding.
- You have any allergies to this drug or its ingredients

Even though some of the above may appear obvious, it is important that your doctor is aware if any of them apply to you**.**

Trifluoperazine 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 these tasks.

Effects on Newborns:
In some cases, babies born to a mother taking Trifluoperazine during pregnancy have experienced symptoms that are severe and require the baby to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your baby if he

has difficulty breathing, is very sleepy, has muscle stiffness, or floppy muscles (like a rag doll), is shaking, or is having difficulty feeding.

People who take Trifluoperazine are cautioned:

- **Against exposure to extreme heat**
- **That drugs such as Trifluoperazine 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 Trifluoperazine.**

INTERACTIONS WITH THIS MEDICATION

Trifluoperazine can add to the effects of alcohol. You should avoid consuming alcoholic beverages while on Trifluoperazine 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 Trifluoperazine, 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 Trifluoperazine if you have drowsiness caused by other medications.

Drugs that may interact with Trifluoperazine include:

- anti-anxiety agents,
- antidepressants,
- anti-seizure medicine,
- high blood pressure medicine,
- cabergoline, lithium,
- cisapride,
- atropine-like drugs,
- narcotic pain relievers (e.g., codeine),
- drugs used to aid sleep,
- drowsiness-causing antihistamines or other drugs (e.g., diphenhydramine),
- metrizamide,
- anaesthetics used prior to surgery.
- medicines for Parkinson's disease (e.g. levodopa).
- blood thinning medicines (anticoagulants such as warfarin).
- antacids used to treat indigestion.
- medicines for psychiatric conditions (neuroleptics)
- heart medicines which prolong the QT interval (e.g. quinidine, disopyramide, procainamide, amiodarone, sotalol)
- drugs causing electrolyte imbalances (e.g. diuretics)

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 interaction with Trifluoperazine.

PROPER USE OF THIS MEDICATION

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

Your doctor will decide which dose is best for you.

Usual dose:

Adults:

Trifluoperazine is usually taken twice-a-day. Patients with mild to moderate symptoms usually start with 1 or 2 mg twice-a-day. If necessary, dosage may be increased to 6 mg daily but above this amount, side effects are more likely to occur in some patients.

Patients with moderate to severe symptoms can start with 5 mg 2 or 3 times-a-day. Dosage can be increased gradually; the average maintenance dose is 15 to 20 mg per day. Some patients may require more.

Children:

It is administered once or twice a day, in a dosage adjusted to the condition and the weight of the child. Dosage may be gradually increased until symptoms are controlled or until side effects become troublesome. The lowest effective dosage should always be used. In most cases, it is not necessary to exceed 15 mg of trifluoperazine daily.

Trifluoperazine is not indicated for children younger than 6 years of age.

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.

Symptoms of overdose include muscle twitching, drowsiness, weakness, tremor, irregular heartbeat, low blood pressure, agitation, and confusion, dizziness, increased salivation, trouble swallowing, loss of balance or coordination, and fainting.

Missed Dose:
If you miss a dose, wait until your next dose. Do not take the dose you have missed. You can then carry on as before. Do not take more than one dose at a time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

[The narrative part of this section should include a brief summary of self-limiting side effects. Serious side effects should be included in the table that follows and do not need to be discussed in the narrative text. This explains most of the deletions.]

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

Side effects may include: sweating, urinary incontinence, dizziness, drowsiness, dry mouth, nasal congestion, nausea and vomiting, headache, menstrual changes, change in libido, swelling of the breasts and milk production in both men and women, weight changes and blurred vision. Very rarely, patients may experience a fast or irregular heartbeat, constipation, difficulty or inability to pass urine or a high temperature.

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

Your doctor should take blood tests before starting Trifluoperazine. 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 notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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.		√	

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
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.			√
	Tardive Dyskinesia: uncontrollable movements or twitches of the body, face, eyes or tongue, stretching the neck and body.		√	
	Akathisia: a feeling of restlessness, inability to remain motionless		√	
	Fast or irregular heartbeat.		√	
	High Blood Pressure: headaches, vision disorders, nausea and vomiting.		√	
	Low Blood Pressure: feeling of Lightheadedness or fainting especially when getting up from a lying or sitting position		√	
	Decreased sweating		√	
	Seizures or fits.			√

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
	Painful erection lasting longer than 4 hours			√
	Jaundice: yellow color to skin and eyes, dark urine.		√	
	Vision Changes: blurred vision, glaucoma or other eye disorder.		√	
	Drowsiness, dizziness, skin reactions, dry mouth, stimulation, insomnia, fatigue, weakness, anorexia, amenorrhea, lactation and blurred vision may be seen occasionally.		√	
	Increased Blood Sugar: frequent urination, thirst and hunger	√		

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

HOW TO STORE IT

Store TRIFLUOPERAZINE at room temperature (15°C-30°C) in well closed containers. Protect from light.

Do not use after the expiry date shown on the bottle. Keep this medication 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.

MORE INFORMATION

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

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

1-877-998-9097

This leaflet was prepared by AA Pharma Inc.

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