

**PRESCRIBING INFORMATION**

**TRIFLUOPERAZINE**

**Trifluoperazine Tablets BP**

**1, 2, 5, 10 and 20 mg**

**Antianxiety-Antiemetic-Antipsychotic**

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**THERAPEUTIC CLASSIFICATION**

Antianxiety-Antiemetic-Antipsychotic

**ACTIONS AND CLINICAL PHARMACOLOGY**

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.

### **INDICATIONS AND CLINICAL USE**

Anxiety states: It controls excessive anxiety, tension and agitation seen in neuroses or associated with somatic conditions.

The treatment or prevention of nausea and vomiting of various causes.

The 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.

### **CONTRAINDICATIONS**

Comatose or greatly depressed states due to CNS depressants; blood dyscrasias, bone marrow depression; liver damage.

### **WARNINGS**

Patients who have demonstrated a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) with a phenothiazine should not be re-exposed to any phenothiazine, including trifluoperazine, unless, in the judgment of the physician, the potential benefits of treatment outweigh the possible hazard.

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).

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.

### **PRECAUTIONS**

Clinical experience has demonstrated that trifluoperazine has a wide margin of safety. However, 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.

Geriatrics and Debilitated Patients: Care should be exercised in treating elderly or debilitated patients as some appear prone to neurological adverse reactions.

Phenothiazines can produce alpha-adrenergic blockade. Because hypotension has occurred, large doses and parenteral administration should be avoided in patients with impaired

cardiovascular systems. To further minimize the occurrence of hypotension after initial injection, keep patient lying down and observe for at least 0.5 hour. If hypotension occurs from parenteral or oral dosing, 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.

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

Certain 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 pigmentation and ocular changes 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.

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

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 drug accumulation, patients on long-term therapy, particularly on high doses, should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

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.

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.

Drug Interactions: Phenothiazines may diminish the effect of oral anticoagulants.

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. As with other phenothiazine derivatives, 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.

### Pregnancy

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.

While it is generally recognized that caution should always be observed when prescribing for the pregnant patient, especially during the first trimester, if the physician considers that antiemetic or tranquilizer therapy is necessary for the welfare of the patient, then trifluoperazine is indicated.

### Lactation

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

## **ADVERSE REACTIONS**

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.

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 reinstated, it should be a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstated. In most cases, barbiturates by suitable route of administration will suffice. In more severe cases the administration of an antiparkinsonism agent (**except levodopa**) usually produces rapid reversal of symptoms. 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. If this condition becomes too troublesome, the symptoms can be controlled by dosage reduction or concomitant administration of a barbiturate.

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. There is typically no loss of consciousness and definite prodromata are usually present. 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 or a barbiturate is often sufficient. In moderate cases, barbiturates will usually bring rapid relief. In more severe adult cases, the administration of an antiparkinsonism agent, **except levodopa**, usually produces rapid reversal of symptoms. Also,



i.v. diphenhydramine or caffeine with sodium benzoate seems to be effective. In children, reassurance and barbiturates 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 readily 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: In rare instances, this syndrome may occur 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 of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. If there is a reinstatement 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.

ECG Changes: 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.

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Primarily involvement of the extrapyramidal mechanism producing some of the dystonic reactions to a more marked degree. 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.

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, e.g., i.v. fluids and/or vasoconstrictors. 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.

If administration of a stimulant is desirable, amphetamine or caffeine with sodium benzoate is recommended. Stimulants that may cause convulsions (e.g., picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinsonism drugs (**except levodopa**), barbiturates or diphenhydramine.

Limited experience indicates that phenothiazines are **not** dialyzable.

### **DOSAGE AND ADMINISTRATION**

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.

General Practice: Oral: The usual starting dosage is a 1 mg or 2 mg tablet twice daily. In everyday practice it is seldom necessary to exceed 6 mg daily. Because of the inherent long action of trifluoperazine most patients can be effectively controlled on a convenient twice-a-day dosage regimen, and some have been maintained on once-a-day administration.

Office Psychiatric Practice: Neurotics and other patients with symptoms of anxiety: The dosage information given for the use of trifluoperazine in everyday practice is, generally speaking,

applicable to the treatment of nonhospitalized psychiatric patients with relatively mild mental and emotional disturbances.

Released patients: Psychiatric patients recently discharged from the hospital or on convalescent leave should continue with the maintenance dosage determined during hospitalization.

Patients with moderate to Severe Symptoms: In borderline psychotics and in other nonhospitalized psychiatric patients with moderate to severe symptoms, the recommended starting dose is 2 to 4 mg twice daily. (Small or emaciated patients should always be started on the lower dosage.) The dosage should be increased gradually as necessary, until symptoms are controlled. The majority of patients will show optimum response on 15 to 20 mg daily, although a few patients will require 40 mg or more per day. In most cases, optimum dosage levels are reached within 2 or 3 weeks after the start of therapy.

If side effects become bothersome during the period of dosage adjustment, they can usually be controlled promptly by concomitant administration of an antiparkinsonism agent (**not levodopa**). Some physicians prefer to administer an antiparkinsonism agent prophylactically in all patients whose daily dosage level reaches 10 mg or more.

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

Hospitalized Adult Psychiatric Patients: The usual starting dose is a 5 mg tablet administered orally 2 or 3 times daily. (Small or emaciated patients should be started on a 2 mg tablet 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. Although some

patients have been given 80 mg or more daily, 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. In some chronic refractory patients, this period may extend from several months to a year.

Psychotic Children: The dosages given below apply to children ages 6 to 12, who are either hospitalized or under adequate supervision.

The usual starting dose is a 1 mg tablet administered once or twice daily, depending on the size of the child. 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 size of the child 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. However, some older children with severe symptoms may require, and be able to tolerate, higher dosages.

#### **AVAILABILITY OF DOSAGE FORMS**

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.