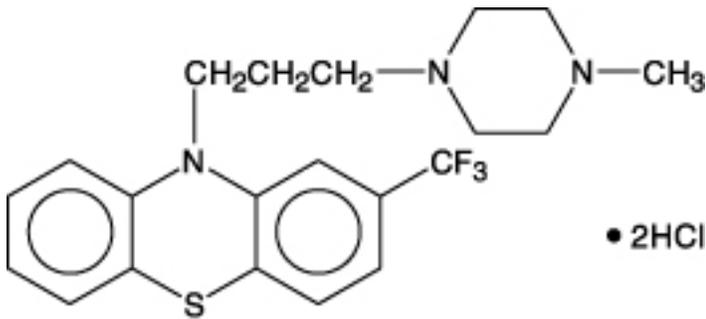


TRIFLUOPERAZINE - trifluoperazine hydrochloride tablet, film coated
Stat Rx USA

DESCRIPTION

Each tablet for oral administration contains trifluoperazine hydrochloride equivalent to 1 mg, 2 mg, 5 mg, or 10 mg trifluoperazine. The structural formula is:



Inactive ingredients: D and C Red #30 Aluminum Lake, FD and C Blue #2 Aluminum Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose (monohydrate), magnesium stearate, polyethylene glycol, povidone, starch (corn), and titanium dioxide.

INDICATIONS AND USAGE

For the management of schizophrenia.

Trifluoperazine HCl is effective for the short-term treatment of generalized non-psychotic anxiety. However, trifluoperazine HCl is not the first drug to be used in therapy for most patients with non-psychotic anxiety because certain risks associated with its use are not shared by common alternative treatments (i.e., benzodiazepines).

When used in the treatment of non-psychotic anxiety, trifluoperazine HCl should not be administered at doses of more than 6 mg per day or for longer than 12 weeks because the use of trifluoperazine HCl at higher doses or for longer intervals may cause persistent tardive dyskinesia that may prove irreversible (see **WARNINGS**).

The effectiveness of trifluoperazine HCl as a treatment for non-psychotic anxiety was established in a four-week clinical multicenter study of outpatients with generalized anxiety disorder (DSM-III). This evidence does not predict that trifluoperazine HCl will be useful in patients with other non-psychotic conditions in which anxiety, or signs that mimic anxiety, are found (i.e., physical illness, organic mental conditions, agitated depression, character pathologies, etc.).

Trifluoperazine HCl has not been shown effective in the management of behavioral complications in patients with mental retardation.

CONTRAINDICATIONS

A known hypersensitivity to phenothiazines, comatose or greatly depressed states due to central nervous system depressants and, in cases of existing blood dyscrasias, bone marrow depression and pre-existing liver damage.

WARNINGSTardive Dyskinesia

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

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to neuroleptic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on

PRECAUTIONS and ADVERSE REACTIONS.

Neuroleptic Malignant Syndrome (NMS)

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

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

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

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

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration of lithium and neuroleptics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome (NMS).

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 HCl, unless in the judgment of the physician, the potential benefits of treatment outweigh the possible hazard.

Trifluoperazine HCl may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, caution patients 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 the drug, the possibility of an undesirable additive depressant effect should be considered.

Usage In Pregnancy

Safety for the use of trifluoperazine HCl during pregnancy has not been established. Therefore, it is not recommended that the drug be given to pregnant patients except when, in the judgment of the physician, it is essential. The potential benefits should clearly outweigh possible hazards. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

Reproductive studies in rats given over 600 times the human dose showed an increased incidence of malformations above controls and reduced litter size and weight linked to maternal toxicity. These effects were not observed at half this dosage. No adverse effect on fetal development was observed in rabbits given 700 times the human dose nor in monkeys given 25 times the human dose.

Nursing Mothers

There is evidence that phenothiazines are excreted in the breast milk of nursing mothers. Because of the potential for serious adverse reactions in nursing infants from trifluoperazine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

PRECAUTIONS General

Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Thrombocytopenia and anemia have been reported in patients receiving the drug. Agranulocytosis and pancytopenia have also been reported – warn patients to report the sudden appearance of sore throat or other signs of infection. If white blood cell and differential counts indicate cellular depression, stop treatment and start antibiotic and other suitable therapy.

Jaundice of the cholestatic type of hepatitis or liver damage has been reported. If fever with gripe-like symptoms occurs, appropriate liver studies should be conducted. If tests indicate an abnormality, stop treatment.

One result of therapy may be an increase in mental and physical activity. For example, a few patients with angina pectoris have complained of increased pain while taking the drug. Therefore, angina patients should be observed carefully and, if an unfavorable response is noted, the drug should be withdrawn.

Because hypotension has occurred, large doses and parenteral administration should be avoided in patients with impaired cardiovascular systems. To minimize the occurrence of hypotension after injection, keep patient lying down and observe for at least 1/2 hour. If hypotension occurs from parenteral or oral dosing, place patient in head-low position with legs raised. If a vasoconstrictor is required, norepinephrine bitartrate and phenylephrine HCl are suitable. Other pressor agents, including epinephrine, should not be used as they may cause a paradoxical further lowering of blood pressure.

Since certain phenothiazines have been reported to produce retinopathy, the drug should be discontinued if ophthalmoscopic examination or visual field studies should demonstrate retinal changes.

An antiemetic action of trifluoperazine HCl may mask the signs and symptoms of toxicity or overdosage of other drugs and may obscure the diagnosis and treatment of other 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 central nervous system or vasomotor symptoms, should be kept in mind.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Because phenothiazines may interfere with thermoregulatory mechanisms, use with caution in persons who will be exposed to extreme heat.

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

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.

Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concurrently.

Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

Phenothiazines may lower the convulsive threshold; dosage adjustments 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 which lower the seizure threshold, including phenothiazine derivatives, should not be used with metrizamide. As with other phenothiazine derivatives, trifluoperazine HCl should be discontinued at least 48 hours before myelography, should not be resumed for at least 24 hours postprocedure, and should not be used for the control of nausea and vomiting occurring either prior to myelography or postprocedure with metrizamide.

The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Long-Term Therapy

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 neuroleptics should be evaluated periodically to decide whether the maintenance dosage could be lowered or drug therapy discontinued.

ADVERSE REACTIONS

Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision and neuromuscular (extrapyramidal) reactions.

Extrapyramidal Symptoms

These symptoms are seen in a significant number of hospitalized mental patients. They may be characterized by motor restlessness, be of the dystonic type, or they may resemble parkinsonism.

Depending on the severity of symptoms, dosage should be reduced or discontinued. If therapy is reinstated, it should be at 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. (Or, injectable diphenhydramine hydrochloride may be useful.) In more severe cases, the administration of an anti-parkinsonism agent, except levodopa, usually produces rapid reversal of symptoms. Suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed.

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

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 phase becomes too troublesome, the symptoms can usually be controlled by a reduction of dosage or change of drug. Treatment with anti-parkinsonian agents, benzodiazepines or propranolol may be helpful.

Pseudo-parkinsonism

Symptoms may include: mask-like facies; drooling, tremors; pill-rolling motion; cogwheel rigidity; and shuffling gait. Reassurance and sedation are important. In most cases, these symptoms are readily controlled when an anti-parkinsonism agent is administered concomitantly. Anti-parkinsonism agents should be used only when required. Generally, therapy of a few weeks to two to three months will suffice. After this time patients should be evaluated to determine their need for continued treatment. (Note: Levodopa

has not been found effective in pseudo-parkinsonism.) Occasionally it is necessary to lower the dosage of trifluoperazine HCl or to discontinue the drug.

Tardive Dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. The syndrome can also develop, although much less frequently, after relatively brief treatment periods at low doses. This syndrome appears in all age groups. Although its prevalence appears to be highest among elderly patients, especially elderly women, it is impossible to rely upon prevalence estimates to predict at the inception of neuroleptic treatment which patients are likely to develop the syndrome. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. In rare instances, these involuntary movements of the extremities are the only manifestations of tardive dyskinesia. A variant of tardive dyskinesia, tardive dystonia, has also been described.

There is no known effective treatment for tardive dyskinesia; anti-parkinsonism agents do not alleviate the symptoms of this syndrome. If clinically feasible, it is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or 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.

Adverse Reactions Reported with Trifluoperazine HCl or Other Phenothiazine Derivatives

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, or occur with greater intensity, in patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines.

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

Not all of the following adverse reactions have been observed with every phenothiazine derivative, but they have been reported with one or more and should be borne in mind when drugs of this class are administered: extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) some of which have lasted months and even years – particularly in elderly patients with previous brain damage; grand mal and petit mal convulsions, particularly in patients with EEG abnormalities or history of such disorders; altered cerebrospinal fluid proteins; cerebral edema; intensification and prolongation of the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, organophosphorus insecticides; autonomic reactions (dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis); reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia, hemolytic anemia, aplastic anemia); liver damage (jaundice, biliary stasis); endocrine disturbances (hyperglycemia, hypoglycemia, glycosuria, lactation, galactorrhea, gynecomastia, menstrual irregularities, false positive pregnancy tests); skin disorders (photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes – particularly nonspecific, usually reversible Q and T wave distortions – have been observed in some patients receiving phenothiazine tranquilizers. 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.

Note: There have been occasional reports of sudden death in patients receiving phenothiazines. In some cases, the cause appeared to be cardiac arrest or asphyxia due to failure of the cough reflex.

OVERDOSAGE

(See also under **ADVERSE REACTIONS**)

DOSAGE AND ADMINISTRATIONAdults

Dosage should be adjusted to the needs of the individual. The lowest effective dosage should always be used. Dosage should be increased more gradually in debilitated or emaciated patients. When maximum response is achieved, dosage may be reduced gradually to a maintenance level. Because of the inherent long action of the drug, patients may be controlled on convenient b.i.d. administration; some patients may be maintained on once-a-day administration.

When trifluoperazine HCl is administered by intramuscular injection, equivalent oral dosage may be substituted once symptoms have been controlled.

Note: Although there is little likelihood of contact dermatitis due to the drug, persons with known sensitivity to phenothiazine drugs should avoid direct contact.

Elderly Patients

In general, dosages in the lower range are sufficient for most elderly patients. Since they appear to be more susceptible to hypotension and neuromuscular reactions, such patients should be observed closely. Dosage should be tailored to the individual, response carefully monitored, and dosage adjusted accordingly. Dosage should be increased more gradually in elderly patients.

Non-psychotic Anxiety

Usual dosage is 1 or 2 mg twice daily. Do not administer at doses of more than 6 mg per day or for longer than 12 weeks.

Psychotic Disorders

ORAL: Usual starting dosage is 2 mg to 5 mg b.i.d. (Small or emaciated patients should always be started on the lower dosage).

Most patients will show optimum response on 15 mg or 20 mg daily, although a few may require 40 mg a day or more. Optimum therapeutic dosage levels should be reached within two or three weeks.

Psychotic Children

Dosage should be adjusted to the weight of the child and the severity of the symptoms. These dosages are for children ages 6 to 12, who are hospitalized or under close supervision.

ORAL: The starting dosage is 1 mg administered once a day or b.i.d. Dosage may be increased gradually until symptoms are controlled or until side effects become troublesome.

While it is usually not necessary to exceed dosages of 15 mg daily, some older children with severe symptoms may require higher dosages.

HOW SUPPLIED

Trifluoperazine hydrochloride tablets, USP are available as:

1 mg: Round, film-coated, lavender colored tablets, debossed GG 51 on one side and 1 on the reverse side, and supplied as:

NDC 0781-1030-01 bottles of 100

NDC 0781-1030-05 bottles of 500

NDC 0781-1030-10 bottles of 1000

NDC 0781-1030-13 unit dose packages of 100

2 mg: Round, film-coated, lavender colored tablets, debossed GG 53 on one side and 2 on the reverse side, and supplied as:

NDC 0781-1032-01 bottles of 100

NDC 0781-1032-05 bottles of 500

NDC 0781-1032-10 bottles of 1000

NDC 0781-1032-13 unit dose packages of 100

5 mg: Round, film-coated, lavender colored tablets, debossed GG 55 on one side and 5 on the reverse side, and supplied as:

NDC 0781-1034-01 bottles of 100

NDC 0781-1034-05 bottles of 500

NDC 0781-1034-10 bottles of 1000

NDC 0781-1034-13 unit dose packages of 100

This strength tablet for use only in severe neuropsychiatric conditions.

10 mg: Round, film-coated, lavender colored tablets, debossed GG 58 on one side and 10 on the reverse side, and supplied as:

NDC 0781-1036-01 bottles of 100

NDC 0781-1036-05 bottles of 500

NDC 0781-1036-10 bottles of 1000

NDC 0781-1036-13 unit dose packages of 100

This strength tablet for use only in severe neuropsychiatric conditions.

Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature). Protect from moisture.

Dispense in a tight, light-resistant container.

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Sandoz Inc.

Princeton, NJ 08540

trifluoperazine2mg

Packaged and distributed by: **STAT Rx USA**, Gainesville, GA 30501

Trifluoperazine
2mg 30 Tabs

Generic For:
NDC 16590-305-30 Prod# 305-30 Lot# SAMPLE

Each Tablet Contains: Trifluoperazine (as the hydrochloride) 2mg USP

Mfg By: Sandoz Inc., Princeton, NJ 08540 NDC 0781-1032-01

Mfg Lot: 182972 Discard After: 12/10 MD 11/24/2009 9621958

AM CZH

Caution: Federal law prohibits transfer of this drug to any person other than the individual for whom it was prescribed. May cause DROWSINESS. ALCOHOL may intensify this effect. Use care when operating dangerous machinery. May cause Nausea, Headaches, Dizziness, Constipation and Dry Mouth.

16590-305-30

RX ONLY-KEEP OUT OF REACH OF CHILDREN