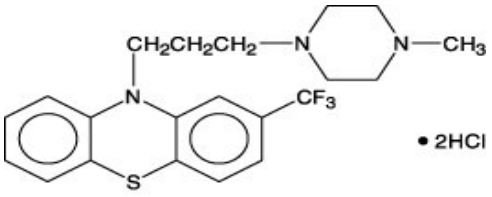
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

TRINICALM PLUS
(Trifluoperazine + Benzhexol Hydrochloride tablets)

COMPOSITION

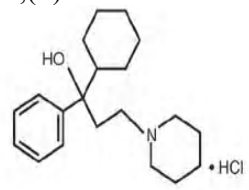
Each uncoated tablet contains :
Trifluoperazine Hydrochloride I.P equivalent to Trifluoperazine 5mg
Benzhexol Hydrochloride I.P. 2mg
Color : Indigo Carmine

Trifluoperazine is chemicaly 10-H -Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)-, dihydrochloride.
The structural formula is:



$C_{21}H_{24}F_3N_3S \bullet 2HCl$ M.W. 480.42

Benzhexol Hydrochloride is a white or slightly off white, crystalline powder, having not more than a very faint odor.
Benzhexol Hydrochloride is the substituted piperidine salt, 1-piperidinepropanol,α-cyclohexyl-α-phenyl-,hydrochloride,(±)-. The structural formula is:



$C_{20}H_{31}NO \bullet HCl$ M.W. = 337.93

CLINICAL PHARMACOLOGY

Mechanism of Action:

Trifluoperazine

Trifluoperazine is a Piperazine Phenothiazine tranquiliser with potent anti-psychotic, anxiolytic and antiemetic activity, and a pharmacological profile of moderate sedative and hypotensive properties, and fairly pronounced tendency to cause extrapyramidal reactions.

Benzhexol Hydrochloride

Benzhexol hydrochloride resembles atropine in its peripheral actions on autonomic effector cells, having an inhibitory effect on the parasympathetic nervous system. It is one half as active as atropine on smooth muscle and one third as active as a mydriatic. It

possesses about one tenth the potency of atropine on salivary glands and cardiac-vagal mechanisms. On the C.N.S., the actions of benzhexol likewise resembles those of atropine.

PHARMACOKINETICS:
Trifluoperazine is well absorbed but undergoes extensive first pass metabolism. Distribution is wide and elimination occurs in the bile and urine. Inactive ingredients in the tablets include sucrose.
Benzhexol is well absorbed from the gastro-intestinal tract.

INDICATIONS AND USAGE
Treatment of symptoms and prevention of relapse in schizophrenia and in other psychoses, especially of the paranoid type, but not in depressive psychoses. It may also be used as an adjunct in the short-term management of severe psychomotor agitation and of dangerously impulsive behaviour in, for example, mental subnormality.
Benzhexol is used for the symptomatic control of all forms of Parkinsonism, including the postencephalitic arteriosclerotic, and idiopathic types. It favourably influences rigidity and akinesia in the majority of patients. Tremor is generally improved also, but in some instances of severe rigidity, the tremor may be accentuated when the rigidity is diminished. Benzhexol favourably effects mood and reduces salivation.

CONTRAINDICATIONS
TRIFLUOPERAZINE:
Do not use trifluoperazine in comatose patients, particularly is associated with other central nervous system depressants. Do not use trifluoperazine in those patients with existing blood dyscrasias or known liver damage, or in those hypersensitive to trifluoperazine, related compounds, or any of the excipients. Patients with uncontrolled cardiac decompensation should not be given trifluoperazine.
BENZHEXOL HYDROCHLORIDE:
Benzhexol hydrochloride should not be given to patients with closed-angle glaucoma or to patients with a narrow angle between the iris and the cornea since its use may increase the intra-ocular pressure. The drug is contra-indicated in patients suffering from a paralytic ileus.

WARNINGS AND PRECAUTIONS:
Trifluoperazine:
Trifluoperazine should be discontinued as the first sign of clinical symptoms of tardive dyskinesia and Neuroleptic Malignant Syndrome.
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.
Care should be taken when treating elderly patients, and the initial dosage should be reduced. Such patients can be especially sensitive, particularly to extrapyramidal and hypotensive effects. Patients with cardiovascular disease including arrhythmias should also be treated with caution. Because trifluoperazine may increase activity, care should be taken in patients with angina pectoris. If an increase in pain is noted, the drug should be discontinued. Patients who have demonstrated bone marrow suppression or jaundice with

a phenothiazine should not be re-exposed to 'Trifluoperazine (or any trifluoperazine) unless in the judgement of the physician the potential benefits of treatment outweigh the possible hazard.
In patients with Parkinson's disease, symptoms may be worsened, and the effects of levodopa reversed. Since phenothiazines may lower the convulsive threshold, patients with epilepsy should be treated with caution, and metrizamide avoided. Although trifluoperazine has minimal anticholinergic activity, this should be borne in mind when treating patients with narrow angle glaucoma, myasthenia gravis or prostatic hypertrophy.
Nausea and vomiting as a sign of organic disease may be masked by the anti-emetic action of trifluoperazine.
Acute withdrawal symptoms including nausea, vomiting and insomnia have been described after abrupt cessation of high doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, a gradual withdrawal is advisable.
Phenothiazines should be used with care in extremes of temperature since they may affect body temperature control.
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Trifluoperazine and preventive measures undertaken

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.
Trifluoperazine is not licensed for the treatment of dementia-related behavioral disturbances.

BENZHEXOL:

Anticholinergic medications, including benzhexol, should not be withdrawn abruptly in patients on long-term therapy, to avoid recurrence of the original symptoms and possible anticholinergic rebound. Prescribers should be aware that benzhexol may be the subject of abuse due to its euphoric or hallucinogenic properties.
Since atropine-like drugs may cause psychiatric symptoms such as confusion, delusion and hallucinations, benzhexol should be used with extreme caution in elderly patients.
As benzhexol may provoke or exacerbate tardive dyskinesia, it is not recommended for use in patients with this condition.
Since benzhexol has been associated with clinical worsening of myasthenia gravis, the drug should be avoided or used with great caution in patients with myasthenia gravis.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsoprtion or sucrase-maltase insufficiency should not take this medicine.

PREGNANCY & LACTATION:

Trifluoperazine:

Trifluoperazine has been available since 1958. There are some animal studies that indicate a teratogenic effect, but results are conflicting. There is no clinical evidence

(including follow-up surveys in over 800 women who had taken low-dosage trifluoperazine during pregnancy) to indicate that trifluoperazine has a teratogenic effect in man. Nevertheless, drug treatment should be avoided in pregnancy unless essential, especially during the first trimester. Trifluoperazine crosses the placenta and passes into the milk of lactating dogs; breast feeding should only be allowed at the discretion of the physician.

BENZHEXOL:

Pregnancy

There is inadequate information regarding the use of benzhexol in pregnancy. Animal studies are insufficient with regard to effects on pregnancy, embryonal/foetal development, parturition and postnatal development. The potential risk for humans is unknown. Benzhexol should not be used during pregnancy unless clearly necessary.

Lactation

It is unknown whether benzhexol is excreted in human breast milk. The excretion of benzhexol in milk has not been studied in animals. Infants may be very sensitive to the effects of antimuscarinic medications. Benzhexol should not be used during breast feeding.

ADVERSE REACTIONS:

TRIFLUOPERAZINE:

Lassitude, drowsiness, dizziness, transient restlessness, insomnia, dry mouth, blurred vision, muscular weakness, anorexia, mild postural hypotension, skin reactions including photosensitivity reactions, weight gain, oedema and confusion may occasionally occur. Tachycardia, constipation, urinary hesitancy and retention, and hyperpyrexia have been reported very rarely. Adverse reactions tend to be dose-related and to disappear.

Hyperprolactinaemia may occur at higher dosages with associated effects such as galactorrhoea, amenorrhoea or gynaecomastia; certain hormone-dependent breast neoplasms may be affected. Phenothiazines can produce ECG changes with prolongation of the QT interval and T-wave changes; serious arrhythmias have been reported. Such effects are rare with trifluoperazine.

In some patients, especially non-psychotic patients, trifluoperazine even at low dosage may cause unpleasant symptoms of being dulled or, paradoxically, of being agitated.

Extrapyramidal symptoms are rare at oral daily dosages of 6 mg or less; they are considerably more common at higher dosage levels. These symptoms include parkinsonism; akathisia, with motor restlessness and difficulty in sitting still; and acute dystonia or dyskinesia, which may occur early in treatment and may present with torticollis, facial grimacing, trismus, tongue protrusion and abnormal eye movements including oculogyric crises. These effects are likely to be particularly severe in children. Such reactions may often be controlled by reducing the dosage or by stopping medication. In more severe dystonic reactions, an anticholinergic antiparkinsonism drug should be given.

Tardive dyskinesia of the facial muscles, sometimes with involuntary movements of the extremities, has occurred in some patients on long-term, high-dosage and, more rarely, low-dosage phenothiazine therapy, including trifluoperazine. Symptoms may appear for the first time either during or after a course of treatment; they may become worse when treatment is stopped. The symptoms may persist for many months or even years, and

while they gradually disappear in some patients, they appear to be permanent in others. Patients have most commonly been elderly, female or with organic brain damage. Particular caution should be observed in treating such patients.
If tardive dyskinesia occurs, trifluoperazine should be discontinued. Anticholinergic antiparkinsonism agents may aggravate the condition. Since the occurrence of tardive dyskinesia may be related to length of treatment and total cumulative dosage, trifluoperazine should be given for as short a time and at as low a dosage as possible.
The neuroleptic malignant syndrome is a rare but occasionally fatal complication of treatment with neuroleptic drugs, and is characterised by hyperpyrexia, muscle rigidity, altered consciousness and autonomic instability. Intensive symptomatic treatment, following discontinuation of trifluoperazine, should include cooling. Intravenous dantrolene has been suggested for muscle rigidity.
Cholestatic jaundice, and blood dyscrasias such as agranulocytosis, pancytopenia, leucopenia and thrombocytopenia have been reported very rarely. Signs of persistent infection should be investigated.
Very rare cases of skin pigmentation, retinopathy and lenticular opacities have been reported with trifluoperazine. Withdrawal reactions have been reported in association with antipyschotic drugs.
Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs- Frequency unknown

BENZHEXOL HYDROCHLORIDE:
5 to 10% of patients cannot tolerate fully effective doses. Side-effects such as dry mouth and blurred vision are not uncommon. Dizziness, mild nausea or nervousness may be experienced by 30 to 50 per cent of patients on benzhexol. The reactions may be less pronounced as treatment continues. Suppurative parotitis skin rashes dilation of the colon, paralytic ileus, and delusions and hallucinations occur rarely. Patients with arteriosclerosis or with idiosyncrasy may show mental confusion, agitation nausea and vomiting. Potential side-effects associated with the use of any atropine-like drugs include constipation, drowsiness, urinary hesitancy or retention, tachycardia, dilation of the pupil, increased intra-ocular tension, weakness, and headache. Occasionally giddiness and staggering occurs. Large doses may cause cerebral stimulation. When intolerable side-effects occur with doses that fail to control the motor symptoms of the disease, other drugs must be employed along with benzhexol, or the agents must be withdrawn. Caution should be observed when benzhexol is administered to patients with prostatic enlargement, coronary insufficiency, or cardiac failure. Tachycardia may result from vagal inhibition and induce angina of effort in patients with coronary heart disease. The effects of benzhexol and other parasympatholytics may be enhanced by the concomitant administration of other drugs with parasympatholytic properties, such as some antihistamines and phenothiazines and tricyclic antidepressants.

DRUG INTERACTIONS
TRIFLUOPERAZINE:
Potentiation may occur if antipsychotic drugs are combined with CNS depressants such as alcohol, hypnotics, anaesthetics and strong analgesics, or with antihypertensives or other drugs with hypotensive activity, anticholinergics or antidepressants. Phenothiazines may antagonise the action of levodopa. Avoid drugs that depress leucopoiesis.

Serum levels of phenothiazine can be reduced to non-therapeutic concentrations by concurrent administration of lithium. Desferrioxamine should not be used in combination with trifluoperazine, since prolonged unconsciousness has occurred after combination with the related prochiorperazine.
Trifluoperazine may diminish the effect of oral anticoagulants.
Severe extrapyramidal side-effects or neurotoxicity have been observed in patients concurrently treated with lithium and trifluoperazine. Sleep walking has been described in some patients taking phenothiazines and lithium.
Antacids can reduce the absorption of phenothiazines.

BENZHEXOL:

Monoamine oxidase inhibitors (MAOI's), antihistamines, disopyramide, phenothiazines and tricyclic antidepressants increase the side effects of blurred vision and dry mouth, constipation, urinary retention. MAOI's, amantidine and some tricyclic antidepressents may also cause excitation, confusion and hallucination.

DOSAGE AND ADMINISTRATION:

TRIFLUOPERAZINE:-

Dosage:

Adults: The recommended starting dose for physically fit adults is one tablet of Trinicalm Plus twice a day; after a week this may be increased to three tablets a day. If necessary, further increases of one tablet may be made at three-day intervals, but not more often. When satisfactory control has been achieved, dosage should be reduced gradually until an effective maintenance level has been established.
As with all major tranquillisers clinical improvement may not be evident for several weeks after starting treatment, and there may also be delay before recurrence of symptoms after stopping treatment. Gradual withdrawal from high-dosage treatment is advisable.

OVERDOSE

Trifluoperazine:

Signs and symptoms will be predominantly extrapyramidal; hypotension may occur. Absorption of trifluoperazine from the 'Spansule' capsule is likely to be prolonged and this should be borne in mind. Treatment consists of gastric lavage together with supportive and symptomatic measures. Do not induce vomiting. Extrapyramidal symptoms may be treated with an anticholinergic antiparkinsonism drug. Treat hypotension with fluid replacement; if severe or persistent, noradrenaline may be considered. Adrenaline is contra-indicated.

Benzhexol Hydrochloride:

Tachycardia, rapid or stertorous respiration, hyperpyrexia, restlessness, confusion and excitement, and hallucinations passing into delirium. In case of overdosage, treatment is symptomatic and supportive.

Expiry date

Do not use later than date of expiry.

Storage

Keep in a dry place, protected from light.

Presentation

TRINICALM PLUS is available in strip pack of 10 tablets

Marketed by:
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Revised May 2013