SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trifluoperazine 1mg/5ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml dose contains 1 mg trifluoperazine present as the hydrochloride.

Excipients with known effect:
This medicine contains 2.5 mg sodium benzoate (E 211) in each 5 ml dose.
This medicine contains 500.0 mg Sorbitol (E420) in each 5 ml dose.

3 PHARMACEUTICAL FORM

A clear-colourless solution with peach odour

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Low dosage: Trifluoperazine is indicated as an adjunct in the short-term management of anxiety states, depressive symptoms secondary to anxiety and agitation. Orally it is also indicated in the symptomatic treatment of nausea and vomiting.

High dosage: Trifluoperazine is intended for the 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 short-term management of severe psychomotor agitation and of dangerously impulsive behaviour in, for example, mental subnormality.

4.2 Posology and method of administration

Posology
Adults:
Low dosage: 2-4 mg a day given in divided doses, according to the severity of the patient's condition. If necessary, dosage may be increased to 6 mg a day, but above this level extrapyramidal symptoms are more likely to occur in some patients.

High dosage: The recommended starting dosage for physically fit adults is 5 mg twice a day after a week this may be increased to 15 mg a day. If necessary, further increases of 5 mg 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 be delay before recurrence of symptoms after stopping treatment. Gradual withdrawal from high dosage treatment is advisable.

Paediatric population

Low dosage: For children 3-5 years, up to 1 mg a day given in divided doses. For children aged 6-12 years, the dosage may be increased to a maximum of 4 mg a day.

High dosage: For children aged under 12 years, the initial oral dosage should not exceed 5 mg a day, given in divided doses. Any subsequent increase should be made with caution, at intervals of not less than three days, and taking into account age, body weight and severity of symptoms.

Elderly
Reduce starting dose in elderly or frail patients by at least half.

Method of Administration:

Oral.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Do not use Trifluoperazine in comatose patients, particularly if associated with other central nervous system depressants.
- Do not use Trifluoperazine in those with existing blood dyscrasias, or known liver damage.
- Patients with uncontrolled cardiac decompensation should not be given Trifluoperazine.

4.4 Special warnings and precautions for use

Trifluoperazine should be discontinued at 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 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.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. Trifluoperazine should be used with caution in patients with risk factors for stroke.

Caution should be used in patients with cardiovascular disease or family history of QT prolongation. Concomitant use of neuroleptics should be avoided.

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

Acute withdrawal symptoms, including nausea, vomitting, sweating, and insomnia have been described after abrupt cessation 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, gradual withdrawl is advisable.

Phenothiazines should be used with care in extremes of temperature since they may affect body temperature control.

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 behavioural disturbances.

This medicine contains less than 1 mmol sodium (23 mg) per 5 mL dose, i.e. essentially “sodium-free”.

This medicine contains 0.5 mg sodium benzoate in each 1 ml oral solution, which is equivalent to 2.5 mg/5 ml.

This medicine contains 100.0 mg sorbitol in each 1 mL of oral solution, which is equivalent to 500.0 mg per 5 mL dose.

This medicine contains Sorbitol, which is a sugar. If you have been told by your doctor that you are intolerant to some sugars, contact your doctor before taking this medicine. Sorbitol can also cause stomach upset and diarrhoea in some patients.

4.5 Interaction with other medicinal products and other forms of interaction

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 guanethidine and levodopa**.** Trifluoperazine may aggravate Parkinsonism and antagonise the action of levodopa. They may lower the convulsive threshold. Hence patients with epilepsy should be treated with caution.

Serum levels of phenothiazine can be reduced to non-therapeutic concentrations by concurrent administration of lithium. Dosage increases may be needed.

Desferrioxamine should not be used in combination with Trifluoperazine, since prolonged unconsciousness has occurred after combination with the related prochlorperazine.

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.

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.

Phenothiazines increase the risk of ventricular arrhythmias when given with drugs which prolong the Q-T interval; drugs causing electrolyte imbalances.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Neonates exposed to antipsychotics (including Trifluoperazine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding

Trifluoperazine crosses the placenta and passes into the milk of lactating dogs; breast feeding should only be allowed at the discretion of the physician.

4.7 Effects on ability to drive and use machines

Trifluoperazine may cause side effects including drowsiness, dizziness and visual disturbances which interfere with the ability to drive and operate machinery. Do not drive or use machines when you first start to take this medicine until you are certain that you are not getting these side effects.

4.8 Undesirable effects

The following undesirable effects may occur with the use of Trifluoperazine in the following frequencies:

Rare (≥1/10,000 to <1/1,000);

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

The following effects have been reported and are listed below by body system:

System organ class	Frequency	Undesirable effects

Blood and lymphatic system disorders	Very rare	Blood dyscrasias[6] such as agranulocytosis, pancytopenia, leucopenia and thrombocytopenia
Endocrine disorders	Not known	Hyperprolactinaemia[1], galactorrhoea[1], amenorrhoea[1], gynaecomastia[1]
Metabolism and nutrition disorders	Not known	Anorexia, weight gain
Psychiatric disorders	Not known	Unpleasant symptoms[2], Confusion,
Nervous system disorders	Rare	Extrapyramidal symptoms[3], Neuroleptic malignant syndrome[4],
	Not known	Tardive dyskinesia[5], drowsiness, dizziness, transient restlessness, insomnia,
Eye disorders	Very rare	Retinopathy, lenticular opacities
	Not known	Blurred vision
Cardiac disorders	Very rare	Tachycardia
	Rare	Serious arrhythmias, sudden unexplained
		death, cardiac arrest Torsades de pointes
Vascular disorders	Not known	Mild postural hypotension, venous
		thromboembolism, pulmonary
		embolism, deep vein thrombosis
Gastrointestinal disorders	Rare	Extrapyramidal symptoms
		Dry mouth
	Not known	
		Constipation
	Very rare	
Hepatobiliary disorders	Very rare	Cholestatic jaundice
Skin and subcutaneous	Not known	Photosensitivity reactions,
Musculoskeletal and connective tissue disorders	Not known	Muscular weakness
Renal and urinary disorders	Very rare	Urinary hesitancy and retention
Pregnancy, puerperium and perinatal conditions	Not known	Drug withdrawal syndrome neonatal
General disorders and administration site conditions	Not known	Lassitude, oedema, Withdrawal reactions
	Very rare	Hyperpyrexia
Investigations	Rare	ECG changes with prolongation of the QT interval and T-wave changes

Adverse reactions tend to be dose-related and to disappear.

[1]Hyperprolactinaemia may occur at higher dosages with associated effects such as galactorrhoea, amenorrhoea or gynaecomastia; certain hormone-dependent breast neoplasms may be affected.

[2]Trifluoperazine even at low dosage may cause unpleasant symptoms of being dulled or, paradoxically, of being agitated.

[3]Extrapyramidal symptoms are rare at daily oral 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.

[4]The neuroleptic malignant syndrome is a rare but occasionally fatal complication of treatment with various 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.

[5]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. Periodic gradual reduction of dosage to reveal persisting dyskinesia has been suggested, so that treatment may be stopped if necessary. 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.

[6]Signs of persistent infection should be investigated.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Signs and symptoms will be predominantly extrapyramidal; hypotension may occur.

Management

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 contraindicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Phenothiazine antipsychotics

ATC Code: N05AB06

Trifluoperazine is a piperazine phenothiazine tranquilliser with potent antipsychotic, anxiolytic, and anti-emetic activity, and a pharmacological profile of moderate sedative and hypotensive properties, and fairly pronounced tendency to cause extrapyramidal reactions.

5.2 Pharmacokinetic properties

Absorption and Metabolism

Trifluoperazine is well absorbed but undergoes extensive first pass metabolism.

Distribution and Elimination
Distribution is wide and elimination occurs in the bile and urine.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate
Sorbitol
Sucralose
Citric acid, anhydrous
Citric acid Monohydrate
Sodium citrate
Peach flavor (PF-765-335-7) (contains Ethyl acetate, Acetic acid and 2-hexen-1-o)
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years unopened. Once the bottle is opened use within 30 days.

6.4 Special precautions for storage

Store below 25 °C. Keep bottle in the original carton to protect from light.

6.5 Nature and contents of container

Amber (Type III) glass bottle of 200 mL fill volume, closed with a white child-resistant polypropylene closure consisting of a polypropylene outer cap, polypropylene inner cap, polyethylene liner, and tamper-evident ring.

Each pack contains a 5 mL CE-marked dosing syringe with intermediate graduations of 0.1 mL and a “press-in” bottle adaptor.

The bottle, adaptor, syringe, and leaflet are supplied in a cardboard carton.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/1038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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