SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trifluoperazine 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 6mg of trifluoperazine hydrochloride equivalent to 5mg of trifluoperazine

Excipient with known effect: Each tablet contains 91.20 mg of lactose and 50.0 mg of sugar.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sugar coated tablet.

Pea green sugar coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trifluoperazine is a tranquillizer of the phenothiazine group.

In low doses, is indicated:

1. As adjunctive short-term treatment of anxiety states, depressive symptoms secondary to anxiety and agitation.

2. In the symptomatic treatment of nausea and vomiting.

In high doses, is indicated:

3. In schizophrenia and in other psychoses, especially of the paranoid type (but not in depressive psychoses), for the treatment of symptoms, and prevention of relapse.

4 As adjunctive treatment of severe psychomotor agitation, and in cases of mental subnormality where dangerous impulsive behaviour may occur.

4.2 Posology and method of administration

Posology

Adult low dosage (anxiety, nausea, vomiting)

2-4mg daily in divided dosage, to maximum of 6mg daily.

Adult high dosage (psychoses)

Initial:	5 mg twice daily.
After 1 week:	May be increased to 15 mg daily. If necessary, for adequate control further increases of 5 mg daily may be made at 3 day intervals. When satisfactory control has been achieved dosage should be reduced gradually to an effective maintenance level.

Paediatric population

Child low dosage (anxiety, nausea, vomiting)

Age 3-5 Years	Syrup dosage form recommended.
6-12 years	Up to a maximum 4 mg daily in divided doses.

Child high dosage (psychoses)

Age under 12 years:	Initially up to 5 mg daily in divided doses. Any increase should be given cautiously, not more often than every three days, and be adjusted according to age, body weight, and response.

Use in the 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, or related compounds or to any of the excipients listed in section 6.1.
- Antipsychotic drugs may be contraindicated in comatose state, particularly if associated with other central nervous system depressants.
- CNS depression, phaeochromocytoma, existing blood dyscrasias and known liver damage.
- Patients with uncontrolled cardiac decompensation.

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.

Clinical improvement may not occur for several weeks after treatment has started. Similarly, there may be delay in recurrence of symptoms after treatment has stopped.

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. Phenothiazines may affect the body temperature control.

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 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.

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 Tablets and preventive measures undertaken

Acute withdrawal symptoms, including nausea, vomiting, 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, dystona 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.

Patients with known or with a family history of cardiovascular disease or QT prolongation should receive ECG screening, and monitoring and correction of electrolyte imbalance prior to considering treatment with trifluoperazine therapy. Concomitant use of neuroleptics should be avoided.

<u>Increased Mortality in Elderly people with Dementia</u>

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Trifluoperazine may potentiate the effects of alcohol, anaesthetics, hypnotics, strong analgesics, 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.

Avoid drugs that depress leucopoiesis. Desferrioxamine should not be used in combination with trifluoperazine, since prolonged unconsciousness has occurred after combination with the related prochlorperazine

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

Anticoagulants

Trifluoperazine may diminish the effect of oral anticoagulants.

ACE inhibitors and angiotensin-II Antogonists: Severe postural hypotension with chlorpromazine and possibly other phenothiazines.

Antacids and adsorbents: reduced absorption of phenothiazines with antacids and possibly kaolin; reduced absorption of sulpride with antacids.

Antidiabetics: hypoglycaemic effect of sulphonylureas possibly antagonised by phenothiazines.

Antiepileptics: antagonism (convulsion threshold lowered); Carbamazepine accelerates metabolism of clozapine, haloperidol, olanzapine, and risperidone (reduced plasma concentrations); phenytoin accelerates metabolism of clozapine and quetiapine; phenobarbital accelerates metabolism of haloperidol (reduced plasma concentrations).

Other Antipsychotics: increased risk of ventricular arrhythmias with thioridazine and other pimozide, and with pimozide and phenothiazines (avoid concomitant use).

Anxiolytics and hypnotics: enhanced sedative effect; diazepam increases plasma concentrations of zotepine; buspirone increases plasma concentration of haloperidol.

Beta blockers: phenothiazines and pimozide increase the risk of ventricular arrhythmias with sotolol; concomitant administration of propanolol and chlorpromazine may increase plasma concentration of both drugs.

Calcium-channel blockers: Enhanced hypontensive effect Desferrioxamine: manufacturer advices avoid prochlorperazine.

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

Increased risk of extrapyramidal effects and possibility of neurotoxicity with clozapine, haloperidol and phenothiazines.; increased risk of Extrapyramidal effects with sulpride; increased risk of ventricular arrhythmias with thiordazine – avoid concomitant use.

Metoclopramide and Domperidone: Increased risk of extrapyramidal effects with metoclopramide.

Sibutramine: Increased risk of CNS toxicity.

Sympathomimetics: antagonise pressor action.

Tetrabenazine: increased risk of extrapyramidal effects.

Ulcer-healing Drugs: Cimetidine may enhance effects of chlorpromazine, clozapine and possibly other antipsychotics; reduced absorption of sulpride with sucralfate.

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.

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. However, unless treatment is essential, its use should be avoided, 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 doctor.

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

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.

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

Hyperprolactinaemia may occur at higher doses with associated effects e.g. galactorrhoea, amenorrhoea and gynaecomastia; certain hormone-dependent breast neoplasms may be affected.

Phenothiazine can produce ECG changes with prolongation of the QT interval and T wave changes; serious ventricular arrhythmias (VF, VT (rare)), sudden unexplained death; cardiac arrest and Torsades de pointes 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.

May cause patient to feel mentally duller, or in some cases, agitated.

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.

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.

Mild cholestatic jaundice, 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, and lenticular opacities have been reported with Trifluoperazine.

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 automatic instability.

Pregnancy, puerperium and perinatal conditions-Drug withdrawal syndrome neonatal (see section 4.6) -frequency not known.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs-Frequency unknown

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Signs and symptoms will be predominantly extrapyramidal; hypotension may occur. Treatment consists of gastric lavage together with supportive and symptomatic measures. Do not induce vomiting. Extrapyramidal symptoms may be treated with an anticholinergic antiparkinsomsm drug. Treat hypotension with fluid replacement; if severe or persistent, noradrenaline may be considered. Adrenaline is contra-indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Phenothiazine with Piperazine structure

ATC code: N05AB

Mechanism of action and pharmacodynamic effects

Trifluoperazine has a depressant action on the central nervous system and alpha-adrenergic blocking and weaker anticholinergic activities. It is a dopamine inhibator; it inhibits prolactin-release-inhibitory factor, considered to be dopamine, thus stimulating the release of prolactin. The turnover of dopamine in the brain is also increased.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

Trifluoperazine is readily absorbed from the gastro-intestinal tract but is subject to considerable first-pass metabolism in the gut wall. It is also extensively metabolised in the liver and is excreted in the urine and faeces in the form of numerous active and inactive metabolites; there is evidence of enterohepatic recycling.

There is a very wide intersubject variation in plasma concentrations of trifluoperazine; no simple correlation has been found between plasma concentration of trifluoperazine and its metabolites, and their therapeutic effect. Paths of metabolism include hydroxylation and conjugation with glucuronic acid, n-oxidation, oxidation of a sulphur atom and dealkylation.

5.3 Preclinical safety data

None available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Starch

Lactose

Pregelatinised Starch

Sodium Starch Glycollate

Water

Colloidal Anhydrous Silica

Magnesium Stearate

Coating

Opagloss (dry basis)

Sugar

Povidone

Purified Talc

Titanium Dioxide

Opalux ASF *5899* (dry basis) E171, E104, E131, E172

Beeswax Carnuba Wax

6.2 Incompatibilities

No major incompatibilities have been reported, other than those in 4.5 above.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a cool dry place.

6.5 Nature and contents of container

Polypropylene tubular contalner with an open end equipped to accept a polyethylene closure with a tamper-evident tear strip in pack sizes of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 250, 500, 1000 and 5000.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clydesdale Pharma Ltd

Unit 3-4 Campbell Court
Campbell Road
Tadley
RG26 5EG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 51718/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/03/2006

10 DATE OF REVISION OF THE TEXT

27/04/2020