SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trifluoperazine Tablets BP 1mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains trifluoperazine hydrochloride BP 1.2mg equivalent to trifluoperazine 1mg.

Excipients with known effect

Lactose
Sucrose
Sodium benzoate (E211)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablets for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In low dosage, trifluoperazine is indicated as an adjunct in the short-term management of anxiety states, depressive symptoms secondary to anxiety, and agitation. It is also indicated in the symptomatic treatment of nausea and vomiting.

In high dosage, trifluoperazine is indicated 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 the 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:* 2mg to 4mg daily in divided doses according to the severity of the patient's condition. If necessary, dosage may be increased to 6mg daily, but above this level extrapyramidal symptoms are more likely to occur in some patients.

High dosage: The recommended starting dose for physically fit adults is 5mg twice daily; after a week this may be increased to 15mg daily. If necessary, further increases of 5mg may be made at 3-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.

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

Paediatric population: *Low dosage:* For children aged 6-12 years, up to a maximum of 4 mg a day, given in divided doses.

High dosage: For children aged under 12 years, the initial oral dosage should not exceed 5mg 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, bodyweight and severity of symptoms.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, related compounds, 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 patients 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 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 antiemetic 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, 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.

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.

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

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains up to 0.8 mg benzoate salt in each tablet.

Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

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 levodopa. Avoid drugs that depress leucopoiesis. Trifluoperazine may aggravate Parkinsonism and antagonise the action of levodopa. It 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.

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 absorption of phenothiazines.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Fertility

No data available.

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 machinery 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:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

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[1] such as agranulocytosis, pancytopenia, leucopenia and thrombocytopenia.

Endocrine disorders	Not known	Hyperprolactinaemia[2], galactorrhoea[2], amenorrhoea[2], gynaecomastia[2].
Metabolism and nutrition disorders	Not known	Anorexia, weight gain.
Psychiatric disorders	Not known	Unpleasant symtoms[3], confusion.
Nervous system disorders	Rare	Extrapyramidal symptoms[4], neuroleptic malignant syndrome[5].
	Not known	Tardive dyskinesia[6], drowsiness, dizziness, transient restlessness, insomnia.
Eye disorders	Very rare	Retinopathy, lenticular opacities.
	Not known	Blurred vision.
Cardiac disorders	Rare	Serious arrhythmias, unexplained death, cardiac arrest and Torsades de pointes.
	Very rare	Tachycardia.
Vascular disorders	Not known	Mild postural hypotension, venous thromboembolism, pulmonary embolism, deep vein thrombosis.
Gastrointestinal disorders	Very rare	Constipation.
	Not known	Dry mouth.
Hepatobiliary disorders	Very rare	Cholestatic jaundice.
Skin and subcutaneous tissue disorders	Very rare	Skin pigmentation.
	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 (see section 4.6).
General disorders and administration site conditions	Very rare	Hyperpyrexia.
	Not known	Lassitude, oedema, withdrawal reactions.
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]Signs of persistent infection should be investigated.

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

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

[4]Extrapyramidal symptoms are rare at oral daily dosages of 6mg 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.

[5]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.

[6]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 dosage, trifluoperazine should be given for as short a time and at as low a dosage as possible.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Signs and symptoms will be predominately 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: Nervous system; Psycholeptics; Antipsychotics; Phenothiazines with piperazine structure, ATC code: N05AB06

Trifluoperazine is a piperazine phenothiazine tranquilliser with potent anti-psychotic, 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 biotransformation

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

No additional data provided. The pre-clinical safety of trifluoperazine is already well documented.

6.1 List of excipients

Corn starch, lactose, polyvinylpyrrolidone, magnesium stearate, talc, Opaseal* (containing industrial methylated spirit, polyvivinyl acetate phthalate, purified water and stearic acid), sucrose, titanium dioxide and Opalux Blue* (containing sucrose, purified water, titanium dioxide, indigo carmine aluminium lake - E132, polyvinylpyrrolidone and sodium benzoate - E211).

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool dry place. Protect from light.

6.5 Nature and contents of container

Securitainers or opaque screw-cap plastic containers or poly-bag lined lever lid tins. Pack sizes - 50, 100, 112, 250, 500 and 1,000.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd,
Unit G4,
Riverside
Industrial Estate,
Riverside Way,
Dartford,
DA1 5BS UK

8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

27/04/2023