SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trifluoperazine 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains trifluoperazine hydrochloride 5.90 mg equivalent to trifluoperazine 5 mg.

Excipient(s) with known effect: Each tablet contains 30 mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Blue coloured, round biconvex film-coated tablet debossed with ‘S5’ on one side and plain on other side. Diameter 7.60mm.

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. It is also indicated in the symptomatic treatment of nausea and vomiting.

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:* 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 dose 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 also be delay before recurrence of symptoms after stopping treatment. Gradual withdrawal from high-dosage treatment is advisable.

Patients with hepatic impairment

This tablet is not to be given in patients with patients with hepatic impairment.

Elderly:

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

Paediatric population

This tablet presentation is unsuitable for children under 12 years, for whom a liquid presentation should be used.

Method of administration

For oral use

4.3 Contraindications

• Hypersensitivity to the active substance 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 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 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 with patients who have 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 antiemetic 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 behavioural disturbances.

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Potentiation may 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. 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.

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.

The combination of lithium and trifluoperazine should only be used with extreme caution. It has been associated with an increased risk of severe extrapyramidal effects and neurotoxicity, with sleep walking described in some patients. However, it has also been noted that serum levels of phenothiazines can be reduced to non-therapeutic concentrations by concurrent lithium administration.

Antacids can reduce the absorption of phenothiazines.

4.6 Fertility, pregnancy and lactation

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.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients who drive or operate machinery should be warned of the possibility of disturbances of the central nervous system.

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).

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
Vascular disorders	Not known	Mild postural hypotension, venous thromboembolism, pulmonary embolism, deep vein thrombosis
Gastrointestinal disorders	Rare	Extrapyramidal symptoms
	Not known	Dry mouth
	Very rare	Constipation
Hepatobiliary disorders	Very rare	Cholestatic jaundice
Skin and subcutaneous tissue disorders	Not known	Photosensitivity reactions
	Very rare	Skin pigmentation
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 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.

[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. 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.

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 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 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 contra-indicated and dobutamine should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotic, ATC code: N05AB06

A piperazine, phenothiazine tranquilliser with potent anti-psychotic, anxiolytic and antiemetic activity, and a pharmacological profile of moderate sedative and hypotensive properties and fairly pronounced tendency to cause extra pyramidal reactions.

5.2 Pharmacokinetic properties

Absorption

Trifluoperazine is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the gut wall.

Owing to the first-pass effect, plasma concentrations following oral administration are much lower than those following intramuscular injection. Moere over, there is very wide intersubject variation in plasma concentration.

Biotransformation

Paths of metabolism include hydroxylation and conjunction with glucuronic acid, N-oxidation, oxidation of a sulphur atom, and de-alkylation.

Distribution

It is extensively bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma.

Elimination

It is also extensively metabolised in the liver and is excreted in the urine and faeces in the form of numerous active and inactive metabolies; there is evidence of enterohepatic recycling.

Together with its metabolites, it crosses the placental barrier and is excreted in the milk. Inactive ingredients in the tablets include sucrose.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core Tablet

Calcium sulphate dihydrate

Sucrose

Maize Starch

Sodium Starch Glycollate

Magnesium stearate (E470b).

Film-coating

Opadry blue-OY-4492

Polyethylene Glycol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original package and protect from light.

6.5 Nature and contents of container

PVC/PVdC-Alu blisters containing 4, 7, 10, 14, 20, 24, 28, 30, 50, 56, 60, 84, 90, 100, 112 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Ltd.

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Leicester, LE19 1WP, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0369

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

10/10/2023