

**TRIFLUOPERAZINE TABLETS BP 10 MG****INDIA****1.3.1 Summary of Product Characteristics (SmPC)****1. Name of Medicinal Product****TRIFLUOPERAZINE TABLETS BP 10 MG****2. Qualitative and Quantitative Composition****2.1. Qualitative declaration:****Composition of the Drug product:**

Each film coated tablet contains:

Trifluoperazine Hydrochloride BP

Equivalent to Trifluoperazine 10 mg

Excipients Q.S.

Colour: Indigo Carmine &amp; Titanium dioxide

**Qualitative & Quantitative Composition Formula:****Batch Size:** 1,00,000 Tablets

| Sr. No. | Name of raw material          | Specification | Label Qty/tab (mg) | Over ages | Qty. per Tab (mg) | Qty. Per Batch (Kg) | Function                      |
|---------|-------------------------------|---------------|--------------------|-----------|-------------------|---------------------|-------------------------------|
| 1.      | Trifluoperazine Hydrochloride | BP            | 10.00              | 16.0 %    | 11.60             | 1.16                | Active                        |
| 2.      | Starch                        | BP            | 50.00              | ---       | 50.00             | 5.00                | Diluent                       |
| 3.      | Lactose                       | BP            | 75.00              | ---       | 75.00             | 7.50                | Diluent                       |
| 4.      | Micro crystalline cellulose   | BP            | 3.00               | ---       | 3.00              | 0.30                | Diluent                       |
| 5.      | Starch                        | BP            | 3.00               | ---       | 3.00              | 0.30                | Binder                        |
| 6.      | Magnesium Stearate            | BP            | 2.00               | ---       | 2.00              | 0.20                | Lubricant                     |
| 7.      | Sodium Starch Glycolate       | BP            | 3.00               | ---       | 3.00              | 0.30                | Disintegrant                  |
| 8.      | Purified Talc                 | BP            | 2.00               | ---       | 2.00              | 0.20                | Diluent & Anti-Sticking Agent |
| 9.      | Fumed Silica                  | BP            | 6.00               | ---       | 6.00              | 0.60                | Glidant                       |

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|                         |                                    |          |      |     |          |          |                     |
|-------------------------|------------------------------------|----------|------|-----|----------|----------|---------------------|
| 10.                     | Hydroxy Propyl Methyl Cellulose    | BP       | 3.00 | --- | 3.00     | 0.30     | Film Forming Agent  |
| 11.                     | Titanium Dioxide                   | BP       | 0.50 | --- | 0.50     | 0.05     | Colouring Agent     |
| 12.                     | Polyethylene Glycol 4000           | BP       | 0.50 | --- | 0.50     | 0.05     | Film Coating Agent  |
| 13.                     | Purified Talc                      | BP       | 0.50 | --- | 0.50     | 0.05     | Anti-Sticking Agent |
| 14.                     | Idacol Indigo Carmine Supra Colour | In House | 0.20 | --- | 0.20     | 0.02     | Colouring Agent     |
| 15.                     | Methylene Chloride*                | BP       | Q.S. | --- | Q.S.     | Q.S.     | Solvent             |
| 16.                     | Iso Propyl Alcohol*                | BP       | Q.S. | --- | Q.S.     | Q.S.     | Solvent             |
| Total Weight of tablets |                                    |          |      |     | 160.0 mg | 16.00 kg |                     |

BP: British Pharmacopoeia

\*Does not present in finished product, evaporated during drying.

**Addition of Overages:** 16.0% of Overages added to Trifluoperazine Hydrochloride to compensate the loss in potency upon storage.**3. Pharmaceutical form**

Film coated Tablets

Light blue coloured round shaped film coated tablet plain on both the sides.

**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.

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**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 will all major tranquillisers clinical improvement may not be evident for several weeks after starting treatment and there may also be a delay before recurrence of symptoms after stopping treatment. Gradual withdrawal from high dosage treatments is advisable.

**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 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 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 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 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.

#### **4.5 Paediatric population**

Potential 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 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.

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 Interaction with other medicinal products and other forms of interaction****Pregnancy**

Trifluoperazine Tablets have 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-dose Trifluoperazine during pregnancy) to indicate that Trifluoperazine has a teratogenic effect on man. Nevertheless, drug treatment should be avoided in pregnancy unless considered 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**

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 ( $\geq 1/10,000$  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 | Very rare | Blood dyscrasias <sup>6</sup> such as agranulocytosis, |



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|   |           |  |
|---|-----------|--|
| disorders                                       |           | pancytopenia, leucopenia and thrombocytopenia  |
| Endocrine disorders                             | Not known | Hyperprolactinaemia <sup>1</sup> , galactorrhoea <sup>1</sup> ,<br>amenorrhoea <sup>1</sup> , gynaecomastia <sup>1</sup> |
| Metabolism and nutrition disorders              | Not known | Anorexia, weight gain  |
| Psychiatric disorders                           | Not known | Unpleasant symptoms <sup>2</sup> , Confusion   |
| Nervous system disorders                        | Rare      | Extrapyramidal symptoms <sup>3</sup> , Neuroleptic malignant syndrome <sup>4</sup>                                       |
|   | Not known | Tardive dyskinesia <sup>5</sup> , 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  |

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|  |           |   |
|--|-----------|---|
| 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.

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

<sup>2</sup>Trifluoperazine even at low dosage may cause unpleasant symptoms of being dulled or, paradoxically, of being agitated.

<sup>3</sup>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.

<sup>4</sup>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.

<sup>5</sup>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

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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.

#### **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: Phenothiazine typical antipsychotics

ATC Code: N05AB06

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 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. Moreover, 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 metabolites; 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**

Preclinical studies undertaken in dogs have demonstrated that trifluoperazine crosses the placenta and passes into the milk of lactating dogs.

**6. PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

| <b>Sr. No.</b> | <b>Ingredients Name</b>            | <b>Specification</b> |
|----------------|------------------------------------|----------------------|
| 1.             | Starch                             | BP                   |
| 2.             | Lactose                            | BP                   |
| 3.             | MCCP                               | BP                   |
| 4.             | Magnesium Stearate                 | BP                   |
| 5.             | Sodium Starch Glycolate            | BP                   |
| 6.             | Purified Talc                      | BP                   |
| 7.             | Fumed Silica                       | BP                   |
| 8.             | Hydroxy Propyl Methyl Cellulose    | BP                   |
| 9.             | Titanium Dioxide                   | BP                   |
| 10.            | Polyethylene Glycol 4000           | BP                   |
| 11.            | Idacol Indigo Carmine Supra Colour | In House             |



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|     |                    |    |
|-----|--------------------|----|
| 12. | Methylene Chloride | BP |
| 13. | Iso Propyl Alcohol | BP |

**6.2 Incompatibilities:** Not Applicable

**6.3 Shelf-life:** 24 Months

**6.4 Special precautions for storage:**

Store in a dark, dry place, Not exceeding 30°C temp.

Keep all medicines out of reach of children.

**6.5 Nature and contents of container:**

1000 tablets are packed in a jar with silica gel pocket and leaflets

**6.6 Special precautions for disposal and other handling**

No special instructions for use/handling

**7- Marketing Authorization Holder:**

**EMBASSY PHARMACEUTICAL & CHEMICALS LTD.**

**41, ADEMOLA STREET, SOUTH WEST IKOYI, LAGOS-NIGERIA.**

**8- Marketing Authorization Number (s):**

**Product license / registration Number (s)**

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**9- Manufacturer Name:**

**SWISS PHARMA PVT.LTD.**

3709, G.I.D.C. Phase IV, Vatva,

Ahmedabad –382445,

Gujarat, India.

**10- Date of first authorization/renewal of the authorization:**

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**11- Date of revision of the text:**

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