STELENZINE® PRODUCT INFORMATION
(trifluoperazine)

NAME OF MEDICINE
Trifluoperazine hydrochloride

CAS: 440-17-5

DESCRIPTION
Trifluoperazine is a white to pale yellow, crystalline powder, hygroscopic, freely soluble in water, soluble in alcohol, practically insoluble in ether which melts at approx. 242°C, with decomposition. Trifluoperazine is a phenothiazine tranquilliser with potent anti-psychotic, anxiolytic and anti-emetic activity.

Formula: C21H24F3N3S.2HCl

MW: 480.4

PHARMACOLOGY
Antagonism of dopamine-mediated synaptic neurotransmission is an important action of neuroleptic drugs including trifluoperazine and is believed to contribute to their antipsychotic action. The antidopaminergic effects are also considered to be responsible for the diverse extrapyramidal manifestations.

INDICATIONS
Chronic Therapy
In higher doses for the management of psychotic disorders, such as acute and chronic schizophrenia, psychosis due to organic brain damage, toxic psychosis, manic depressive psychosis, senile psychosis and psychosis associated with mental deficiency.
Short Term Therapy
For the relief of delusions, hallucinations and confusion, and for the control of tremulousness and aggressive behaviour in alcoholic patients.

In low doses to control excessive anxiety, tension and agitation in non-psychotic disorders. Trifluoperazine is not recommended as first line therapy in patients with non-psychotic anxiety disorders, nor should therapy be carried out for more than 12 weeks.

For nausea and vomiting (see PRECAUTIONS).

CONTRAINDICATIONS
Known hypersensitivity to the drug. Cross sensitivity to other phenothiazines may occur. Comatose or depressed states due to CNS depressants. Circulatory collapse. Phaeochromocytoma. Existing blood dyscrasias, liver disease or bone marrow depression.

PRECAUTIONS
Trifluoperazine should be discontinued at the first sign of clinical symptoms of tardive dyskinesia and Neuroleptic Malignant Syndrome. Tardive dyskinesia and Neuroleptic Malignant Syndrome have been reported in association with anti-psychotic drugs (see ADVERSE REACTIONS).

Elderly Patients with Dementia-related Psychosis
Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include age >80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

Cerebrovascular Adverse Events (CVAE), including Stroke, in Elderly Patients with Dementia
An approximately 3-fold increase of cerebrovascular adverse events has 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. An increased risk cannot be excluded for other antipsychotics or other patient populations. Trifluoperazine should be used with caution in patients with risk factors for stroke.
Prolongation of QT Interval

- Use with caution in patients with cardiovascular disease or family history of QT prolongation.
- Avoid concomitant QT prolonging drugs.

Venous thromboembolism
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 taken.

Parkinson’s disease
Physicians should weigh the risks versus the benefits when prescribing trifluoperazine to patients with Parkinson’s disease or dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome (NMS) as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation and postural instability with frequent falls, in addition to extrapyramidal symptoms.

Suicide
The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany therapy.

Haematological effects
Agranulocytosis, neutropenia, thrombocytopenia, pancytopenia and anaemia have been reported rarely in patients receiving the drug. Haematological monitoring should be carried out as indicated. Patients who have experienced blood dyscrasias with a phenothiazine should not be re-exposed to any phenothiazine, including Stelazine, unless in the judgement of the doctor the potential benefits of treatment outweigh the possible hazards.

Hepatic effects
Jaundice of the cholestatic type of hepatitis or liver damage has been reported. Patients who have experienced bone marrow suppression or jaundice with a phenothiazine should not be re-exposed to any phenothiazine, including Stelazine, unless in the judgement of the doctor the potential benefits of treatment outweigh the possible hazards.
Stimulatory effects
One result of therapy with phenothiazines may be an increase in mental and physical activity. For example, a few patients with angina pectoris have complained of increased pain while taking the drug. Therefore, angina patients should be observed carefully and, if an unfavourable response is noted, the drug should be withdrawn.

Hypotension
In view of the possibility of hypotension, large doses should be avoided in patients with impaired cardiovascular function, or those given spinal or regional anaesthesia. The blood pressure of patients undergoing surgery should be carefully monitored; and lower doses of anaesthetics or CNS depressants may be required.

Phenothiazines may also produce hypotension in phaeochromocytoma patients.

If hypotension occurs, place patient in a head-low position with legs raised. When treating prolonged or severe hypotension, noradrenaline or phenylephrine are the most suitable vasoconstrictor agents. Other pressor agents, including adrenaline, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents, and cause a further lowering of blood pressure.

Ocular effects
Some phenothiazines have been reported to produce retinopathy, lenticular and corneal lesions, especially after long-term treatment with high doses. The drug should be discontinued if ophthalmoscopic examination or visual field studies demonstrate changes.

Anti-emetic effect
The anti-emetic effect of Stelazine may mask signs of overdosage of toxic drugs or obscure the diagnosis of conditions such as intestinal obstruction, brain tumour, and Reye's Syndrome.

Anticholinergic effects
Because of the anticholinergic effects of phenothiazines, they should be used with caution in patients with prostatic hypertrophy.
Attacks of intermittent blurred vision accompanied by pain in the eye necessitate exclusion of the risk of acute glaucoma before commencing therapy. A red, painful eye during treatment with trifluoperazine may mean acute glaucoma which needs urgent ophthalmological consultation. As with all drugs which can exert an anticholinergic effect, trifluoperazine should be used with caution in patients under treatment for glaucoma.

**Prolonged therapy**
With prolonged administration at high dosages, the possibility of cumulative effects, with sudden onset of severe central nervous system or vasomotor symptoms should be kept in mind. It is therefore recommended that patients on long-term therapy at high doses be evaluated periodically to decide whether the maintenance dose could be lowered or drug therapy discontinued.

Temporary withdrawal effects (vertigo, tachycardia, headache, nausea and vomiting) are occasionally observed with sudden cessation of long-term phenothiazine therapy.

**Convulsive threshold**
As phenothiazines may lower the convulsive threshold, dosage adjustment of anti-convulsants may be necessary. Use with caution in patients with epileptic tendencies, EEG abnormalities or subcortical brain damage.

**Other effects**
Neuroleptic drugs may elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescribing of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical nor epidemiological studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumourigenesis; the available evidence is considered too limited to be conclusive at this time.
As phenothiazines may interfere with thermoregulatory mechanisms, use with caution in persons who will be exposed to extreme heat.

Hepatic function, renal function and blood picture should be checked periodically.

Stelazine concentrate contains sodium bisulphate which may cause allergic type reactions including anaphylaxis in certain susceptible people, especially people with a history of asthma or allergy.

Stelazine Liquid Forte contains sodium benzoate.

**Use in the elderly**

Care should be exercised when treating elderly or debilitated patients as they are more susceptible to the neurological and hypotensive side effects of phenothiazines. Dosages in the lower range are recommended. Refer to PRECAUTIONS, Hypotension for the treatment of hypotension should it occur.

**Use in Pregnancy** (Category C)

Safety for the use of Stelazine during pregnancy has not been established.

When given in high doses during late pregnancy, phenothiazines have caused prolonged extrapyramidal disturbances in the child. There are also reports of prolonged jaundice and hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.

**Non-teratogenic class effect:** Neonates exposed to antipsychotic drugs (including trifluoperazine) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring.

Trifluoperazine should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.
**Use in Lactation**
Adequate human data on use during lactation and adequate animal reproduction studies are not available. There is evidence that phenothiazines are excreted in the breast milk of lactating women.

**Use in Children**
Take particular care in administering Stelazine to children with acute illnesses (e.g. chicken pox, CNS infections, measles, gastroenteritis) or dehydration.

**Effect on ability to drive or operate machinery**
Stelazine may impair mental and/or physical abilities, especially during the first few days of therapy. Patients should be cautioned about activities requiring alertness, e.g. driving a car or operating machinery.

**Interactions**
If agents such as sedatives, narcotics, anaesthetics, tricyclic antidepressants, tranquillisers or alcohol are used either simultaneously or successively with trifluoperazine, the possibility of an undesirable additive depressant effect should be considered.

Phenothiazines may diminish the effect of oral anticoagulants.

Phenothiazines can produce alpha-adrenergic blockade. Concomitant administration of propranolol with phenothiazines results in increased plasma levels of both drugs. Antihypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concurrently. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

Phenothiazines may lower the convulsive threshold; anticonvulsant dosage adjustment may be necessary. Potentiation of anticonvulsant effects does not occur, however, phenothiazines may interfere with the metabolism of phenytoin, and thus precipitate phenytoin toxicity.

Phenothiazines may also potentiate the effect of atropine and organophosphate insecticides.
Prolongation of QT interval

Trifluoperazine should only be given with the following if absolutely necessary:

- Concomitant QT prolonging drugs (Examples: Amiodarone, Disopyramide, Procainamide).
- Drugs causing electrolyte imbalance.
- Metabolic inhibitors (Actinomycin D).

**Laboratory tests.** Phenothiazines may cause false positives or elevated values in the following liver function tests: bilirubin, serum AST and serum ALT. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

**ADVERSE REACTIONS**

Adverse reactions with phenothiazines vary in type, frequency and individual sensitivity. Some are dose related and some are more likely to occur in patients with underlying medical conditions.

At low dosage (2 - 4 mg daily) adverse reactions are infrequent, usually minor and transient, and unlikely to affect the course of therapy. Occasional instances of drowsiness, dizziness or stimulation may be observed. Neuromuscular (extrapyramidal) reactions are rare at daily dosages of 6 mg or less.

**Neuromuscular (Extrapyramidal) Reactions**

These reactions are seen in a significant number of hospitalised psychiatric patients. The incidence is greater at high phenothiazine dosages. Three groups of side effects characterised by motor restlessness, pseudo-parkinsonism and dystonia, are all recognised as extrapyramidal in origin, and may occur during the administration of these compounds. The incidence of such side effects varies widely, but is lowest when the drug is increased gradually to an optimal therapeutic level.

Depending on the severity of symptoms, dosage should be reduced or discontinued. If therapy is reinstituted, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstituted. In most cases, diphenhydramine is sufficient. In more severe cases, anti-parkinsonian agents, except levodopa, usually produce rapid control of symptoms. Suitable supportive measures such as maintaining a clear airway and adequate hydration should be employed.
* **Motor Restlessness (Akathisia)**
Signs may include inability to remain still, tapping of feet, agitation and insomnia. Such motor restlessness may closely resemble the original neurotic or psychotic signs and it is important to recognise such side effects for what they are and not to increase dosage until they have disappeared. These reactions may spontaneously resolve. Treatment with dose reduction and/or concomitant administration of an anti-cholinergic agent, benzodiazepine or propranolol may be useful.

* **Pseudo-Parkinsonism**
Signs may include: mask-like faces; drooling; tremors; pillrolling motion; cogwheel rigidity; and shuffling gait. Reassurance and sedation are important. In most cases these symptoms are readily controlled when an anti-parkinsonian agent is administered concomitantly (note: levodopa has not been found effective in pseudo-parkinsonism). Occasionally it is necessary to lower the dosage or to discontinue the drug.

* **Dystonias**
Signs may include spasm of the neck muscles, sometimes progressing to torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crisis and protrusion of the tongue.

These can occur with a single low dose of phenothiazine and tend to occur in young people.

Despite their similarity to signs of such CNS diseases as tetanus, encephalitis or meningitis, particularly in children, these dystonias are readily reversible and need not cause undue alarm. They will usually subside within a few hours, and almost always within 24 to 48 hours, after the drug has been discontinued. Whilst they are usually related to high dosage they may occasionally occur as an idiosyncratic reaction in individuals given relatively low dosage of Stelazine for antiemesis or mild tranquillisation. The signs tend to appear, fade and return again.

In mild cases, reassurance or a sedative is often sufficient. In more severe cases an anti-parkinsonian agent (other than levodopa), repeated if necessary, or injectable diphenhydramine usually produces rapid reversal of dystonic signs.
Tardive Dyskinesia

Tardive dyskinesia may develop in patients on anti-psychotic drugs. The disorder consists of repetitive involuntary movements of the tongue, face, mouth or jaw (e.g. protrusion of the tongue, puffing the cheeks, puckering of the mouth, chewing movements). The trunk and limbs are less frequently involved. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of the drug increases. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses. The risk seems to be greater in elderly patients, especially females.

The syndrome may become clinically recognisable either during treatment, upon dosage reduction, or upon withdrawal of treatment. The dosage of anti-psychotic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder, since the syndrome may be masked by a higher dose. In patients requiring long-term treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought.

There is no known effective treatment for tardive dyskinesia. Anti-parkinsonian agents usually do not alleviate symptoms. It is suggested that anti-psychotic agents be discontinued if symptoms of tardive dyskinesia appear.

Neuroleptic Malignant Syndrome

A potentially fatal syndrome called neuroleptic malignant syndrome has been reported in association with anti-psychotic drugs. The syndrome is characterised by muscular rigidity, fever, hyperthermia, altered consciousness and autonomic instability (e.g. tachycardia, labile blood pressure, profuse sweating, dyspnoea).

The management of neuroleptic malignant syndrome should include immediate discontinuation of anti-psychotic drugs, intensive monitoring and treatment of symptoms, and treatment of any associated medical problems.
Other Adverse Reactions

Not all of the following adverse effects have been seen with every phenothiazine, however they have been reported with use of this drug class.

Central nervous system: drowsiness, dizziness, fatigue, blurred vision, seizures (particularly in patients with EEG abnormalities), altered CSF proteins, cerebral oedema, prolongation of the action of CNS depressants (opiates, alcohol, barbiturates), autonomic reactions (mouth dryness, nasal congestion, headache, nausea, constipation, ileus, impotence, urinary retention, priapism, miosis, and mydriasis), muscular weakness, reactivation of psychotic processes (catatonic-like states), increased aggressiveness, and toxic confusional states.

Cardiovascular: peripheral oedema, ECG changes including non-specific transient Q and T wave abnormalities, QT Prolongation, hypotension, cardiac arrhythmias including atrioventricular block, paroxysmal tachycardia, ventricular fibrillation and cardiac arrest, Ventricular arrhythmias, and Torsades de pointes.

Haematological: blood dyscrasias including pancytopenia, agranulocytosis, thrombocytopenic purpura, leucopenia, eosinophilia, haemolytic anaemia, aplastic anaemia (see PRECAUTIONS).

Hepatic: jaundice, biliary stasis, (see PRECAUTIONS).

Endocrine: hyperglycaemia, hypoglycaemia, glycosuria, lactation, galactorrhoea, gynaecomastia, elevated prolactin levels, amenorrhoea, false positive pregnancy tests.

Dermatological: photosensitivity, erythema, urticarias, pruritus, eczema, skin pigmentation, erythema multiforme, epithelial keratopathy, contact dermatitis in those handling phenothiazines.

Hypersensitivity: bronchospasm, angioedematous oedema, anaphylaxis.

Ocular: blurred vision, pigmentary retinopathy, lenticular and corneal deposits, lacrimation, keratoconjunctivitis.
**Vascular:** There have been reports of increased risk of thromboembolic events such as deep vein thrombosis and pulmonary embolism.

**Other:** fever, increased appetite, weight change, systemic lupus-like syndrome, reversed adrenaline effect.

**Note:** There have been occasional reports of sudden death in patients receiving phenothiazines. In some cases, the cause appeared to be cardiac arrest or asphyxia due to failure of the cough reflex.

**DOSAGE & ADMINISTRATION**
Dosage should be tailored to the individual response, carefully monitored and adjusted accordingly. Because of the inherent long action of the drug, patients may be controlled on convenient twice daily administration. Dosage should be increased more gradually in elderly and debilitated patients.

**For Office Patients and Outpatients**
- **Adults** - Usual dosage is 1 or 2 mg twice daily. If necessary, dosage may be increased to 6 mg daily but above this level extrapyramidal symptoms are more likely to occur in some patients.

- **Children** - For children of 3 - 5 years, up to 1 mg daily in divided doses. For children 6 - 12 years, dose may be increased to a maximum of 4 mg daily according to body weight and general physical condition. Dosage is based on a rate of 1 mg per 20 kg bodyweight per day.

**For Hospitalised Patients or Those under Close Supervision**
- **Adults** - Usual starting dosage is 2 to 5 mg twice daily. The recommended starting dosage for physically fit adults is 5 mg twice a day. Small or emaciated patients should always be started on a lower dosage.

After a week, this may be increased to 15 mg a day in divided doses. If necessary, further increases of 5 mg may be made at 3 day intervals, but not more often. Most patients will show optimum response on 15 to 20 mg daily, although a few will require more. When satisfactory control has been achieved, dosage may be reduced gradually until an effective maintenance level has been established.
Children - For children 6 - 12 years, the starting dosage is 1 mg twice daily. Any subsequent increase should be made with caution at intervals of not less than 3 days and taking into account age, bodyweight and severity of symptoms. It is usually not necessary to exceed dosages of 15 mg daily.

Renal Impairment
Dosage should be adjusted in patients with renal impairment (glomerular filtration rate <50mL/minute).

Notes on Dose Forms
Stelazine Spansule capsules are equivalent mg for mg to Stelazine tablets but require only one dose every 24 hours. Thus, a 15 mg Spansule capsule daily provides the same result as a 5 mg tablet three times daily.

For children, uncooperative patients, and those who have difficulty in taking tablets, Stelazine liquid is often useful. It is pleasantly fruit flavoured and may be disguised in liquid or semi-solid foods.

Although there is little likelihood of contact dermatitis due to the drug, persons with known sensitivity to phenothiazines should avoid direct contact.

OVERDOSAGE
Symptoms
Primarily involvement of the extrapyramidal system producing some of the dystonic reactions to a more marked degree. Symptoms of central nervous system depression to the point of somnolence and coma. Agitation and restlessness may also occur. Other possible manifestations include convulsions, ECG changes and cardiac arrhythmias, fever and autonomic reactions such as hypotension, dry mouth, and ileus.

Treatment
Essentially symptomatic and supportive. Early gastric lavage is recommended. Keep patient under observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage.
Do not attempt to induce emesis because a dystonic reaction of the head or neck may develop that could result in aspiration of vomitus.

Extrapyramidal symptoms may be treated with anti-parkinsonian drugs or diphenhydramine, although this may aggravate any toxic features resulting from the anticholinergic activity of trifluoperazine.

If hypotension occurs, the standard measures for managing circulatory shock should be initiated. If it is desirable to administer a vasoconstrictor, noradrenaline and phenylephrine are most suitable. Other pressor agents, including adrenaline, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents and cause a further lowering of blood pressure (see PRECAUTIONS, Hypotension for treatment of hypotension).

Limited experience indicates that phenothiazines are not dialyzable.

**PRESENTATION AND STORAGE CONDITIONS**

| Tablets 1 mg -       | blue, film-coated tablets, containing trifluoperazine 1mg as the hydrochloride, packs of 100, in bottles and in blister packs in cartons, store below 30°C.  
                         | *Also contains:* calcium sulphate, sucrose, maize starch, gelatin, purified talc, stearic acid, purified water and proprietary ingredient Opadry OY-S-4492. |

| Tablets 2 mg -       | blue, film-coated tablets, containing trifluoperazine 2mg as the hydrochloride, packs of 100, in bottles and in blister packs in cartons, store below 30°C.  
                         | *Also contains:* calcium sulphate, sucrose, maize starch, gelatin, purified talc, stearic acid, purified water and proprietary ingredient Opadry OY-S-4492. |

| Tablets 5 mg -       | blue, film-coated tablets, containing trifluoperazine 5mg as the hydrochloride, packs of 100, in bottles and in blister packs in cartons, store below 30°C.  
                         | *Also contains:* calcium sulphate, sucrose, maize starch, gelatin, purified talc, stearic acid, purified water and proprietary ingredient Opadry OY-S-4492. |
Spansule Capsules - yellow/clear capsules, containing blue and white pellets, containing trifluoperazine 15mg as the hydrochloride, packs of 50 in a jar, store below 30°C.

Also contains: gelatin, maize starch, purified talc, kaolin, sucrose, titanium dioxide, microcrystalline wax, glycercyl distearate, quinoline yellow, indigo carmine, docusate sodium, shellac and iron oxide black.

Liquid Forte - trifluoperazine, 5mg/5mL in bottles of 1L, packs of 10, store below 30°C.

Also contains: sodium benzoate, saccharin sodium, sodium chloride, sodium citrate, citric acid monohydrate, glycerol, sorbitol, purified water, sunset yellow FCF and proprietary ingredients; Natural Soluble Orange Flavour, Sweet and Quassia Q5 Soluble Essence.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF MEDICINE

Schedule 4

DATE OF APPROVAL

Date of TGA approval: 13 September 2006
Date of most recent amendment: 05 November 2015

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