

## New Zealand Data Sheet

# Stelazine®

*Trifluoperazine dihydrochloride*

Tablets 1 mg, 2 mg and 5 mg

Forte Liquid 5 mg/5 mL (NOT CURRENTLY MARKETED)

Spansule 15 mg (NOT CURRENTLY MARKETED)

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## Presentations

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Tablets 1 mg, blue, film coated, biconvex tablets.

Tablets 2 mg, blue, film coated, biconvex tablets.

Tablets 5 mg, blue, film coated, biconvex tablets.

Forte Liquid oral solution, 5 mg/5 mL, clear, viscous liquid with a bitter orange taste.

Spansule modified release capsules 15 mg, size no. 1 hard gelatin capsule with opaque yellow cap and transparent colourless body containing a mixture of dark blue, light blue and white spherical pellets. Both body and cap are printed "15" in black.

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## Indications

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### Chronic Therapy

In high doses for management of manifestations of psychotic disorders, such as acute and chronic catatonic hebephrenic and paranoid schizophrenia, psychosis due to organic brain damage, toxic psychosis, manic depressive psychosis, senile psychosis and mental deficiency.

### Short Term Therapy

Treatment of acute alcoholism for the relief of delusions, hallucinations and confused state, and for the control of accompanying tremulousness and aggressive behaviour.

In low doses to control excessive anxiety, tension and agitation as seen in neuroses or associated with somatic conditions. For nausea and vomiting of various causes.

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## Dosage and Administration

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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.

### For Office Patients and Outpatients

#### Oral - Adults:

Usual dosage is 1 or 2 mg twice a day. 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.

#### Oral – Children:

For children of 3 - 5 years of age, up to 1 mg a day in divided doses.

For children 6 - 12 years of age, the dosage may be increased to a maximum of 4 mg a day according to body weight and general physical condition. Dosage is based on a rate of 1 mg per 20 kg body weight per day.

#### **For hospitalised patients or those under close supervision**

#### Oral - Adults:

Usual starting dosage is 2 mg 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.

#### Oral – 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, body weight and severity of symptoms. It is usually not necessary to exceed dosages of 15 mg daily.

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## **Contraindications**

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Trifluoperazine is contraindicated in:

- cases of known hypersensitivity to trifluoperazine or excipients
- comatose states
- in the presence of large amounts of central nervous system depressants (alcohol, barbiturates, opiates, etc.)
- circulatory collapse
- phaeochromocytoma
- blood dyscrasias, liver disease or bone marrow depression

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## **Warnings and Precautions**

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**Trifluoperazine should be discontinued at the first sign of clinical symptoms of Tardive Dyskinesia or Neuroleptic Malignant Syndrome.**

#### **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.**

### ***Precautions:***

Rare cases of agranulocytosis, neutropenia, pancytopenia, thrombocytopenia, anaemia, jaundice of the cholestatic type of hepatitis or liver damage have been reported in patients receiving high doses of this medicine.

Tardive Dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. The prevalence of the syndrome appears to be highest among the elderly, especially elderly women. The risk of developing the syndrome is believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop after relatively brief treatment periods at low doses. There is no known treatment for established cases of Tardive Dyskinesia, although the syndrome may remit if neuroleptic treatment is withdrawn. Neuroleptic treatment may suppress the signs and symptoms of the syndrome.

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse of blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). The management of NMS should include immediate discontinuation of antipsychotic drugs, and symptomatic treatment. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered.

Patients who have demonstrated blood dyscrasias, 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.

Phenothiazines have been reported to produce retinopathy. The medicine should be discontinued if ophthalmoscopic examination or visual field studies demonstrate retinal changes.

Elderly and debilitated patients appear more prone to hypotension, and to neurological adverse reactions. If hypotension occurs, place patient in head-low position with legs raised. If a vasoconstrictor is required, noradrenaline and phenylephrine are suitable. Other pressor agents including adrenaline, should not be used as they may cause a paradoxical further lowering of blood pressure.

Therapy may result in an increase in mental and physical activity. Patients with angina pectoris should be monitored: if an increase of pain is noted, the medicine should be discontinued.

The antiemetic effect of trifluoperazine may mask signs of overdosage of toxic medicines or obscure the diagnosis of conditions such as intestinal obstruction and brain tumour.

Concomitant administration of trifluoperazine with sedative, narcotics, anaesthetics or alcohol may increase the possibility of an additive depressant effect (see Interactions).

Neuroleptic drugs elevate prolactin levels. Galactorrhea, amenorrhea, gynecomastia and impotence have been reported. However, the clinical significance of elevated serum prolactin levels is unknown.

Phenothiazines may interfere with thermoregulatory mechanisms and should be used with caution in persons who will be exposed to extreme heat.

Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary.

### ***Use in Pregnancy***

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.

Stelazine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### ***Use in Lactation***

There is evidence that phenothiazines are excreted in the breast milk of lactating women.

### ***Effects on Ability to Drive and Use Machines***

Trifluoperazine may cause disturbances of the CNS (see Adverse effects). Patients should be warned of the possible hazards before driving or operating machinery.

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## **Adverse Effects**

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

### **Neuromuscular (Extrapyramidal) Reactions:**

These symptoms are seen in significant numbers of hospitalised mental patients. They may be characterised by motor restlessness, dystonias or may resemble Parkinsonism. The incidence

is greater at higher dosages. Depending on the severity of symptoms, dosage should be reduced or discontinued. If therapy is reinstated, it should be at a lower dosage. Should these symptoms occur in children or pregnant patients, the drug should be stopped and not reinstated. In most cases, a barbiturate or diphenhydramine is sufficient. In more severe cases, anti-Parkinson 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:**

Symptoms may include agitation, jitteriness and sometimes insomnia. These symptoms often disappear spontaneously. Treatment with anti-Parkinson agents, benzodiazepines or propranolol may be useful.

#### **Dystonias:**

Symptoms may include spasm of the neck muscles, torticollis, extensor rigidity of back muscles sometimes progressing to opisthotonos, carpopedal spasm, trismus, difficulty swallowing, oculogyric crisis and protrusion of the tongue. These usually subside in 24 hours after the medicine has been discontinued.

#### **Pseudo-Parkinsonism:**

Symptoms may include mask-like faces, drooling, tremors; pill rolling motion; cog wheel rigidity and shuffling gait. In most cases these symptoms are readily controlled with an anti-Parkinson agent (except levodopa, which has not been found effective).

#### **Tardive Dyskinesia particularly with higher doses:**

As with all antipsychotic agents, persistent Tardive Dyskinesia may occur in some patients on long-term therapy or may appear after drug therapy has been discontinued. The syndrome is characterised by rhythmical involuntary movements of the facial muscles and sometimes of extremities. There is no known effective treatment of Tardive Dyskinesia; anti-Parkinson agents usually do not alleviate the symptoms of this syndrome. Gradual reduction of dosage to reveal persisting dyskinesia has been suggested, so that treatment may be stopped if necessary. See also Warnings and Precautions.

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

#### **Other CNS Reactions:**

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), Neuroleptic Malignant syndrome, muscular weakness.

#### **Cardiovascular:**

Peripheral oedema, ECG changes including non-specific transient Q and T wave abnormalities, QT Prolongation, hypotension, cardiac arrest, ventricular arrhythmias, and Torsades de pointes.

#### **Haematologic:**

Blood dyscrasias, including pancytopenia, agranulocytosis, thrombocytopenic purpura, leukopenia, eosinophilia, haemolytic anaemia, aplastic anaemia.

**Hepatic:**

Jaundice (cholestatic), biliary stasis.

**Endocrine:**

Hyperglycaemia, hypoglycaemia, glycosuria, lactation galactorrhea, gynecomastia, elevated prolactin levels, amenorrhea, false positive pregnancy tests.

**Dermatologic:**

Photosensitivity, erythema, urticarias, eczema, skin pigmentation, epithelial keratopathy.

**Hypersensitivity:**

Bronchospasm, angioneurotic oedema, anaphylaxis.

**Ocular:**

Blurred vision, pigmentary retinopathy, lenticular and corneal deposits.

**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.

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 cough reflex.

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## Interactions

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Trifluoperazine may diminish the effect of oral anticoagulants. Concomitant administration of propranolol with trifluoperazine 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 interact with organophosphate insecticides.

Trifluoperazine may potentiate the action of other CNS depressants.

***Prolongation of QT interval***

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

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

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## Overdose

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Symptoms of overdose are primarily extrapyramidal reactions and symptoms of central nervous system depression. 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 is essentially symptomatic and supportive. Early gastric lavage is recommended. Keep patient under observation and maintain an open airway, since involvement of the extrapyramidal mechanism 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.

For treatment of hypotension (see Warnings and Precautions):

Extrapyramidal symptoms may be treated with anti-Parkinson drugs, barbiturates or diphenhydramine. If administration of a stimulant is desirable, amphetamine, dextroamphetamine or caffeine with sodium benzoate is recommended. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided.

If hypotension occurs, the standard measures for managing circulatory shock should be initiated. If a vasoconstrictor is required, 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.

Limited experience indicates that phenothiazines are not dialyzable.

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## Further Information

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### ***Pharmacodynamic Properties***

Trifluoperazine is a phenothiazine.

The precise mechanism of action has not been determined but may be principally related to the antidopaminergic effects of phenothiazines.

Phenothiazines also have peripheral and/or central antagonistic activity against:

- alpha-adrenergic receptors
- serotonergic receptors
- histaminic (H<sub>1</sub>-receptors)
- and muscarinic receptors.

### ***Pharmacokinetic Properties***

Trifluoperazine:

- undergoes extensive first-pass metabolism
- is highly bound (>99%) in plasma, principally to the alpha<sub>1</sub>-acid glycoprotein.
- has peak concentrations occurring some 1-6 hours after oral dosing with wide variations in plasma concentrations.
- is extensively metabolised, with less than 1% of the dose appearing as unchanged drug in urine.

### ***Preclinical Safety Data***

No further information of relevance.

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## **Pharmaceutical Precautions**

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### ***Incompatibilities***

None identified.

### ***Shelf-life***

Tablets: 3 years

Forte Liquid: 3 years

Spansules: 3 years

### ***Special precautions for storage***

Store below 30°C. Store liquid away from light.

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## **Package Quantities**

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Tablets 1 mg blister packs of 100 tablets

Tablets 2 mg blister packs of 100 tablets

Tablets 5 mg blister packs of 100 tablets

Forte Liquid 5 mg/5 mL bottles of 1000 mL

Spansules 15 mg blister packs of 50 capsules

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## **Medicine Schedule**

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Prescription Medicine

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## **Sponsor Details**

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Boucher & Muir (NZ) Ltd t/a Goldshield Healthcare (NZ)

39 Anzac Road

Browns Bay

Auckland 0753

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## **Date of Preparation**

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9 January 2012