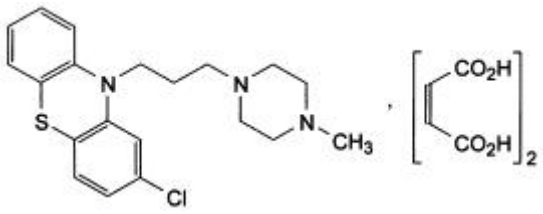
# PRODUCT INFORMATION

**STEMETIL®**

## NAME OF THE MEDICINE

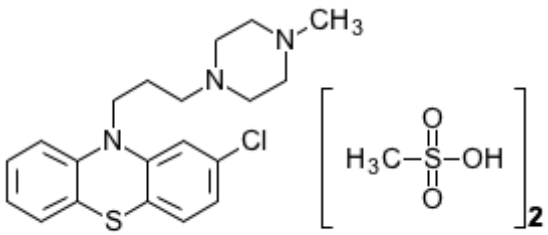
### Australian Approved Name

Tablets



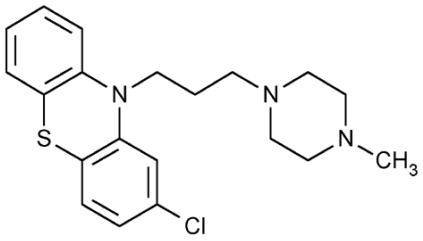
prochlorperazine maleate
Molecular Formula: $C_{20}H_{24}ClN_3S.2C_4H_4O_4$
CAS number: 84-02-6

Injection



prochlorperazine mesilate
Molecular formula: $C_{20}H_{24}ClN_3S.2CH_3SO_3H$
CAS number: 5132-55-8

Suppositories



prochlorperazine base
Molecular Formula: $C_{20}H_{24}ClN_3S$
CAS number: 58-38-8

## DESCRIPTION

Prochlorperazine is 2 chloro-10-(3-(4-methyl piperazinyl)-propyl) phenothiazine. Prochlorperazine maleate contains 62% of the active base; prochlorperazine mesilate contains 66% of the active base.

The maleate is an odourless, nonhydroscopic, white or almost white, fine granular powder, which becomes coloured on exposure to light. It is sparingly soluble (about 0.1%) in water, ethanol or methanol and is insoluble in ether or chloroform.

Stemetil tablets: each tablet contains 5mg prochlorperazine maleate. Excipients are calcium hydrogen phosphate dihydrate, magnesium stearate, sodium lauryl sulfate and wheat starch.

The mesilate is an odourless, nonhydroscopic, almost white, crystalline solid which becomes coloured on exposure to light. It is very soluble in water (more than 2 g/mL) but is only slightly soluble in ethanol or chloroform and is insoluble in ether or benzene. The pH of a 2% aqueous solution is between 2 and 3.

Stemetil injection ampoules: each 1mL ampoule contains 12.5mL prochlorperazine mesilate. Excipients are monoethanolamine, sodium chloride, sodium metabisulfite, sodium sulfite and water for injection.

Stemetil suppositories: The suppositories come in two strengths, 5mg or 25mg. Each suppository contains 5mg or 25mg prochlorperazine maleate. The excipient is hard fat.

## PHARMACOLOGY

Prochlorperazine is a phenothiazine with a piperazine moiety in the side chain. It possesses strong antiemetic and antipsychotic activity with less sedative action than chlorpromazine.

### Pharmacodynamics

As with other phenothiazines, prochlorperazine has actions on several neurotransmitter systems:

1. Antidopamine action, which probably contributes to both the therapeutic effect and unwanted effects including extrapyramidal disorders and endocrine disturbances.
2. $\alpha$-Adrenoreceptor antagonism, which contributes to cardiovascular side effects such as orthostatic hypotension and reflex tachycardia.
3. Potentiation of noradrenaline by blocking its reuptake into nerve terminals.
4. Weak anticholinergic action.
5. Weak antihistamine action.
6. Weak serotonin antagonism.

Prochlorperazine also has an effect on temperature control and blocks conditioned avoidance responses.

### Pharmacokinetics

There are few published data on prochlorperazine pharmacokinetics in the human. Most studies have been done in rats and dose levels do not correspond to those used clinically and metabolic pathways may differ. Similar overall pharmacokinetic patterns however would occur in the human.

Prochlorperazine is well absorbed from the GI tract in rats but absorption is slowed in repeatedly treated animals. The drug is widely distributed to tissues including the brain, fat, kidney, heart and skin and is stored in reticuloendothelial tissues. Phenothiazines are metabolised primarily in the liver and are subject to enterohepatic circulation. Excretion is mainly in the faeces. Only a very small amount (approx. 0.1%) of prochlorperazine and its metabolites are excreted in the first 24 hours in the urine and the drug may continue to be excreted in the urine for up to 3 weeks after cessation of long term therapy. The elimination half-life is approximately 24 hours, presumably due to its enterohepatic circulation.

## INDICATIONS

Nausea and vomiting due to various causes including migraine; vertigo due to Meniere's syndrome, labyrinthitis and other causes.

## CONTRAINDICATIONS

Circulatory collapse, central nervous system depression (coma or drug intoxication), previous history of a hypersensitivity reaction (e.g. jaundice or blood dyscrasia) to phenothiazines especially to prochlorperazine, bone marrow depression.

## PRECAUTIONS

Prochlorperazine should be avoided in patients with renal dysfunction, Parkinson's disease, hypothyroidism, phaeochromocytoma, myasthenia gravis and prostate hypertrophy.

### Hypotension

The autonomic side effects of the piperazine derivatives are less troublesome than those of other phenothiazines, however care should be taken if prochlorperazine is used in the elderly or in patients undergoing surgery with spinal anaesthesia.

### Epileptics

Piperazine derivatives are also less epileptogenic than other phenothiazines, but care should still be exercised in epileptic patients.

**Anticholinergic effects**

Prochlorperazine can cause problems due to anticholinergic effects, especially in the elderly (urinary difficulties, constipation and precipitation of acute narrow angle glaucoma), but to a lesser extent than with other phenothiazines.

**Hypocalcaemia**

It appears from a study of 5 hypocalcaemic patients with hypoparathyroidism that such patients are prone to acute dystonic reactions with prochlorperazine.

**Sedative effect**

Prochlorperazine may impair mental and physical activity especially during the first few days of therapy. Patients should be warned about activities requiring alertness.

**Antiemetic effects**

The antiemetic effects of prochlorperazine may mask signs of overdosage of toxic drugs or obscure the diagnosis of conditions such as intestinal obstruction, brain tumour.

**Reye's Syndrome**

The extrapyramidal symptoms which can occur secondary to prochlorperazine may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g. Reye's Syndrome or other encephalopathy. The use of prochlorperazine and other potential hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's Syndrome.

**Hypothermia**

Severe hypothermia may occur during swimming in cold water or in patients receiving antipyretic therapy.

**Liver disease**

Caution should be used in patients with existing liver disease due to the extensive hepatic metabolism of prochlorperazine. A past history of jaundice resulting from phenothiazine therapy indicates a hypersensitivity reaction and there is a likelihood of cross sensitivity to other phenothiazines.

**Tardive dyskinesia**

Tardive dyskinesia may develop in patients on antipsychotic 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 antipsychotic 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. Antiparkinsonian agents usually do not alleviate symptoms. It is suggested that antipsychotic 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 antipsychotic 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.

**QT Interval**

Very rare cases of QT interval prolongation have been reported with prochlorperazine. Neuroleptic phenothiazines may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death).

QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e., drug induced) QT prolongation. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment (see **ADVERSE EFFECTS).**

**Cerebrovascular Events**

An increased risk of cerebrovascular events has been reported in elderly patients with dementia treated with atypical antipsychotic drugs. An increase in the risk of cerebrovascular events with other antipsychotic drugs or other populations of patients cannot be excluded. Prochlorperazine should therefore be used with caution in patients with stroke risk factors.

**Thromboembolism**

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, prochlorperazine should be used with caution in patients with risk factors for thromboembolism (see **ADVERSE EFFECTS**).

**Elderly Patients with Dementia**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

**Hyperglycaemia**

Hyperglycaemia or intolerance to glucose has been reported in patients treated with prochlorperazine. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on prochlorperazine, should get appropriate glycaemic monitoring during treatment (see **ADVERSE EFFECTS**).

**Injection**

Do not use a darkened solution for injection (more than pale yellow)

**Use in pregnancy (Category C)**

When given in high doses during late pregnancy, phenothiazines have caused jaundice, hyperreflexia, hyporeflexia or prolonged extrapyramidal disturbances in the child. There is evidence of harmful effects in animals. The following effects have been reported (in postmarketing surveillance) in neonates exposed to phenothiazines during the third trimester of pregnancy:

- various degrees of respiratory disorders ranging from tachypnoea to respiratory distress, bradycardia and hypotonia, most often when other drugs such as psychotropic or antimuscarinic drugs were coadministered.
- signs related to the atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, initial feeding difficulties, abdominal bloating, tachycardia;
- neurological disorders such as extrapyramidal symptoms including tremor and hypertonia, somnolence, agitation.

Appropriate monitoring and treatment of neonate born to mothers receiving prochlorperazine is recommended.

Like other drugs it should be avoided in pregnancy unless the physician considers it essential. Neuroleptics may occasionally prolong labour and at such a time should be withheld until the cervix is dilated 3-4 cm. Possible adverse effects on the foetus include lethargy or paradoxical hyperexcitability, tremor and a low Apgar score.

**Use in lactation**

Trace amounts of another phenothiazine, chlorpromazine, have been detected in breast milk, but there is no information available for prochlorperazine. Consequently, it is not known whether it is excreted in breast milk or whether it has a harmful effect on the newborn.

Therefore, prochlorperazine is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

**Use in children**

Prochlorperazine is not recommended for use in children under 10 kg in weight or under 2 years of age as acute extrapyramidal reactions are more likely to occur.

Prochlorperazine should not be given to children by the rectal or intramuscular route.

## INTERACTIONS WITH OTHER MEDICINES

Caution is required with the use of the following medicines due to the risk of QT prolongation (see **PRECAUTIONS**):

- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.
- Other medications such as bepridil, cisapride, sultopride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparfloxacin.
- Medicines which induce bradycardia, such as bradycardia-inducing calcium channel blockers (diltiazem, verapamil), beta-blockers, clonidine, guanfacine, digitalis.
- Medicines which can cause hypokalaemia, such as diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides.
- Other antipsychotics .

Prochlorperazine may enhance the CNS depressant effects of alcohol and other depressant drugs, and potentiate the anticholinergic effects of atropinic agents and tricyclic antidepressants.

Phenothiazines are potent inhibitors of CYP2D6. Co-administration of phenothiazines with amitriptyline, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline. Monitor patients for dose-dependent adverse reactions associated with amitriptyline.

Simultaneous administration of desferrioxamine and prochlorperazine has been observed to induce a transient metabolic encephalopathy characterised by loss of consciousness for 48-72 hours.

Procarbazine has been reported to potentiate the extrapyramidal side effects encountered with the use of prochlorperazine. Phenothiazines have been reported both to impair and increase metabolism of phenytoin, with uncertain clinical significance. Patients on levodopa should not be given phenothiazines because the two drugs are physiologically antagonistic.

Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.

Anithypertensive effects of guanethidine and related compounds may be counteracted when phenothiazines are used concomitantly.

Phenothiazines can diminish the effect of oral anticoagulants. Concomitant administration of propranolol with phenothiazines results in increased plasma levels of both drugs. Phenothiazines may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary.

## ADVERSE EFFECTS

The following reactions have been reported for prochlorperazine or phenothiazines in general.

More common reactions

Gastrointestinal

Constipation, dry mouth.

Nervous System

Drowsiness, akathisia, parkinsonism, (with dyskinesia, tremor and rigidity).

Ocular

Blurred vision.

Less common reactions

Biochemical abnormalities

Elevated serum levels of bilirubin and hepatic enzymes may occur if the patient develops cholestatic jaundice.

Cardiovascular

Hypotension, peripheral oedema, cardiac arrhythmias, ECG changes, QT interval prolongation. There have been isolated reports of sudden death, with possible causes of cardiac origin (see **PRECAUTIONS**), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines. Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs (see **PRECAUTIONS**).

Dermatological

Dermatitis or contact dermatitis, maculopapular eruptions, erythema multiforme, urticaria, photosensitivity, abnormal pigmentation.

Endocrine

Endocrine disturbances including elevated prolactin levels, hyperglycaemia, intolerance to glucose, hypoglycaemia, menstrual irregularities, galactorrhoea, gynaecomastia.

Gastrointestinal

Paralytic ileus.

Genitourinary

Urinary retention, inhibition of ejaculation.

Haematological

Agranulocytosis, atypical lymphocytes, thrombocytopenia, leucopenia, aplastic anaemia.

Hepatic Cholestatic jaundice, liver damage.

Nervous System

Acute dystonic reactions including oculogyric crisis, torticollis and opisthotonus and trismus, seizures, EEG changes, headache, insomnia, catatonia, hyperpyrexia.

Cases of convulsions have been reported.

Ocular

Pigmentary rentinopathy.

Psychiatric

Activation of psychotic symptoms.

Respiratory

Respiratory depression.

Metabolism and Nutrition Disorders

Hyponatraemia and inappropriate antidiuretic hormone secretion have also been reported.

In post-marketing surveillance cases of hyperglycaemia or intolerance to glucose have been reported with antipsychotic phenothiazines (see **PRECAUTIONS**).

Hypersensitivity reactions such as angioedema and urticaria have been reported.

### Serious or Life Threatening Reactions

Prochlorperazine can cause very serious acute dystonic reactions in children leading to cyanosis from laryngospasm, apnoea requiring artificial ventilation, life-threatening tetanus like syndromes, coma and even death. These reactions can occur with a single therapeutic dose. For treatment, see Overdosage. Also, long-term phenothiazine therapy has been associated with ECG changes and life threatening cardiac arrhythmias.

## DOSAGE AND ADMINISTRATION

### Nausea and Vomiting

Adults

If oral administration is not practical, a deep intramuscular injection of 1 mL (12.5 mg) or a 25 mg suppository should be used, followed if required, by normal oral medication six hours later.

Do not use a darkened solution for injection (more than pale yellow).

Dosage should be adjusted to suit the response of the individual, beginning with lowest recommended dosage.

| | |
|---|---|
| Oral: | 5 or 10 mg two or three times daily. |
| Acute: | 20 mg at once, followed, if necessary by 10 mg two hours later. |

Children (See **PRECAUTIONS**, **Use in Children**).

If it is considered unavoidable to use prochlorperazine for a child, the dosage is 250 micrograms/kg bodyweight two or three times a day.

Prochlorperazine has been associated with dystonic reactions particularly after a cumulative dosage of 500 micrograms/kg. It should therefore be used cautiously in children.

Prochlorperazine is not recommended for children weighing less than 10 kg and should not be given to children by the rectal or intramuscular route.

When treating children, it is recommended that the 5 mg tablets are used.

### Vertigo and Meniere's Disease

Adults

| | |
|---|---|
| Oral: | 5 to 10 mg three or four times daily.<br>Dosage may be reduced gradually after several weeks to a maintenance dosage of 5 to 10 mg daily. |

Children

| | |
|---|---|
| Oral: | dose, same as for nausea and vomiting. |

Geriatric

In general, dosages in the lower range are sufficient for most elderly patients. Since they are especially susceptible to hypotension and extrapyramidal reactions, such patients should be observed closely. Dosage should be increased more gradually in elderly patients.

**Impaired Liver Function**

Since prochlorperazine is extensively metabolised by the liver, dosage reduction may be necessary.

## OVERDOSAGE

**Symptoms**

Overdosage with phenothiazines may cause CNS depression progressing from drowsiness to coma with areflexia. Patients with early or mild intoxication may experience restlessness, confusion and excitement.

Other symptoms include hypotension, tachycardia, hypothermia, pupillary constriction, restlessness, tremor, muscle twitching, spasm or rigidity, convulsions, muscular hypotonia, difficulty in swallowing or breathing, cyanosis, and respiratory and/or vasomotor collapse, possibly with sudden apnoea. There is no information available regarding lethal dose in man.

**Treatment**

**1.** Acute dystonic reactions

Intramuscular benztropine (or another antiparkinsonian agent) should be given immediately (adults: 1 to 2 mg i.m., children: 0.2 mg i.m. initially with increments if necessary).

**2.** Overdosage

Emesis should not be induced, not only because the antiemetic action of prochlorperazine prevents the effect of the emetic agent, but also because the sedative and extra-pyramidal side effects increase the risk of pulmonary aspiration should vomiting occur. Management is generally supportive with particular attention to the possibility of obstructed ventilation, severe hypotension, hypothermia, cardiac arrhythmias, convulsions and prolonged deep sedation. Acute dystonic reactions usually occur early (if at all); treatment is with anticholinergic agents, as above.

Adrenaline must not be used as it may cause a paradoxical further lowering of blood pressure

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

## PRESENTATION AND STORAGE CONDITIONS

Stemetil 5 mg tablets are off-white to pale cream coloured circular tablets, not more than slightly mottled or specked, one side impressed with 'S' and reverse face plain.

Stemetil tablets are available in blister packs of 25, 100♦ and 250♦ tablets.

Store below 30°C. Protect from Light.

Stemetil suppositories contain prochlorperazine base equivalent to 5 mg and 25 mg prochlorperazine maleate. Stemetil suppositories are cream, smooth, torpedo-shaped suppositories.

Stemetil suppositories are available in blister packs of 5 suppositories.♦

Store below 25°C. Protect from Light.

Stemetil 12.5 mg/mL solution for injection is clean, bright and not more than very pale yellow. Each ampoule contains 1 mL. Stemetil injection ampoules are available in cartons of 10 ampoules.

Store below 25°C. Protect from Light. Keep ampoules and trays in the carton until time of use.

## NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park NSW  2113

## POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

## DATE OF FIRST INCLUSION IN THE ARTG

21 October 1991

## DATE OF MOST RECENT AMENDMENT

14 August 2017

♦ Not marketed