AUSTRALIAN PRODUCT INFORMATION – STEMZINE® (PROCHLORPERAZINE MALEATE) TABLET

1 NAME OF THE MEDICINE

Prochlorperazine maleate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Stemzine contains 5mg prochlorperazine maleate as the active ingredient.

Excipients of known effect: Gluten.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Stemzine 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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Nausea and vomiting

Adults

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 Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use, Paediatric Use).

Prochlorperazine is not recommended for children under 2 years of age or weighing less than 10 kg.

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.

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

Occasionally the patient may react to the drug with signs of restlessness and excitement; if this occurs, treatment should be discontinued.

Vertigo and Meniere's disease

Adults

Oral: 5 to 10 mg three or four times daily.

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.

4.3 CONTRAINDICATIONS

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

Hypersensitivity to prochlorperazine, other phenothiazines, or to any of the other ingredients listed in Section 6.1.

In children, due to a possible association between use of phenothiazine-containing products and Sudden Infant Death Syndrome (SIDS).

Do not use in paediatric surgery.

Do not use in children for conditions for which dosage has not been established.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions including anaphylactic reaction, urticaria and angioedema have been reported with Stemzine use. In case of allergic reaction, treatment with Stemzine must be discontinued and appropriate symptomatic treatment initiated 4.8 Adverse Effects (Undesirable Effects)).

Prochlorperazine should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis and prostate hypertrophy. It should be avoided in patients with a history of narrow angle glaucoma or agranulocytosis.

Acute withdrawal symptoms, including nausea, vomiting, headache, anxiety, agitation, dyskinesia, dystonia, disturbed temperature regulation, and insomnia, have very rarely been reported following the abrupt cessation of high doses of neuroleptics. Relapse may also occur, and the emergence of extrapyramidal reactions has been reported. Therefore, gradual withdrawal is advisable. Symptoms of withdrawal can occur following treatment at any dose. Withdrawal of treatment should occur under close medical supervision.

As agranulocytosis has been reported, regular monitoring of the complete blood count is recommended. The occurrence of unexplained infections or fever may be evidence of blood dyscrasia and requires immediate haematological investigation.

All patients should be advised that, if they experience fever, sore throat or any other infection, they should inform their physician immediately and undergo a complete blood count. Treatment should be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the blood count.

As with all antipsychotic drugs, Stemzine should not be used alone where depression is predominant. However, it may be combined with antidepressant therapy to treat those conditions in which depression and psychosis coexist.

Prochlorperazine can cause photosensitisation, therefore patients should be advised to avoid exposure to direct sunlight during treatment.

To prevent skin sensitisation in those frequently handling preparations of phenothiazines, the greatest care must be taken to avoid contact of the drug with the skin (see Section 4.8 Adverse Effects (Undesirable Effects)).

In schizophrenia, the response to prochlorperazine treatment may be delayed. If treatment is withdrawn, the reoccurrence of symptoms may not become apparent for some time. Avoid concomitant treatment with other neuroleptics.

Phenothiazines may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, general anesthetics, or alcohol.

Stroke

In randomised clinical trials versus placebo performed in a population with elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patients cannot be excluded. Stemzine should be used with caution with stroke risk factors.

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

Close monitoring is required in patients with epilepsy or a history of seizures, as phenothiazines may lower the seizure threshold. The occurrence of convulsive seizures necessitates the discontinuation of the treatment.

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.

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).

It is imperative that prochlorperazine treatment be discontinued in the event of unexplained fever, as this may be a sign of neuroleptic malignant syndrome (pallor, hyperthermia, autonomic dysfunction, altered consciousness, muscle rigidity).

Signs of autonomic dysfunction, such as sweating and blood pressure instability, may precede the onset of hyperthermia and serve as early warning signs. Although neuroleptic malignant syndrome may be idiosyncratic in origin, dehydration and organic brain disease are predisposing factors (see Section 4.8 Adverse Effects (Undesirable Effects)). 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 Section 4.8 Adverse Effects (Undesirable 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 (VTE), sometimes fatal, 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 Stemzine and preventative measures undertaken. Therefore, prochlorperazine should be used with caution in patients with risk factors for thromboembolism (see Section 4.8 Adverse Effects (Undesirable Effects)).

Hyperglycaemia

Hyperglycaemia or intolerance to glucose has been reported in patients treated with prochlorperazines. 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 Section 4.8 Adverse Effects (Undesirable Effects)).

Alcohol use

Patients are strongly advised not to consume alcohol and alcohol-containing medicines while being treated with Stemzine.

Use in hepatic impairment

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.

Use in the elderly

It should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper-, hypothermia).

Stemzine should be used cautiously in the elderly owing to their susceptibility to drugs acting on the central nervous system and a lower initial dosage is recommended. There is an increased risk of drug-induced Parkinsonism in the elderly particularly after prolonged use. Care should also be taken not to confuse the adverse effects of Stemzine, e.g. orthostatic hypotension, with the effects due to the underlying disorder.

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.

Prolonged administration of any phenothiazine may result in tardive dyskinesias, particularly in the elderly.

Stemzine is not licensed for the treatment of dementia-related behavioural disturbances.

Careful monitoring of treatment with prochlorperazine is required when administered in elderly patients exhibiting greater susceptibility to orthostatic hypotension, sedation, and extrapyramidal effects; chronic constipation (risk of ileus paralytic); possible prostatic hypertrophy.

Paediatric use

(See Section 4.2 Dose and Method of Administration and Section 4.3 Contraindications).

Prochlorperazine should not be used in children under 2 years unless potentially life-saving.

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

Prolonged administration of any phenothiazine may result in tardive dyskinesias, particularly in children.

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

Children with an acute febrile illness (e.g., chickenpox, CNS infection, measles, gastroenteritis) or suffering from dehydration seem to be much more susceptible than adults to neuromuscular reactions, particularly dystonias. In such patients, the drug should be used under close supervision and at low doses.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Contraindicated combinations:

Dopaminergics, except in patients with Parkinson's disease.

Mutual antagonism between dopaminergics and neuroleptics.

Where treatment for neuroleptic-induced extrapyramidal symptoms is required, anticholinergic antiparkinsonian agents should be used in preference to levodopa, since neuroleptics antagonise the antiparkinsonian action of dopaminergics.

Adrenaline must not be used in patients overdosed with Stemzine (see Section 4.9 Overdose).

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

Combinations not recommended or requiring precaution

Dopaminergics in patients with Parkinson’s disease.

Dopaminergics may cause or exacerbate psychotic disorders. If treatment with neuroleptics is required in patients with Parkinson's disease treated with a dopaminergic, the latter should be tapered off gradually (sudden discontinuation of dopaminergic agents exposes the patient to a risk of “neuroleptic malignant syndrome”). For parkinsonian patients who require treatment with both a neuroleptic and a dopaminergic agent, use the minimum effective doses of both medications.

Caution is required with the use of the following medicines due to the risk of QT prolongation (see Section 4.4 Special warnings and precautions for use):

- 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 (amphotericin), glucocorticoids, tetracosactide (tetracosactrin).
- 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. Respiratory depression may occur. Impaired vigilance may make it dangerous to drive or use machines. Avoid consumption of alcoholic beverages and medications containing alcohol.

Anticholinergic agents may reduce the antipsychotic effect of neuroleptics. The mild anticholinergic effect of prochlorperazine may be enhanced by other anticholinergic drugs, possibly leading to dry mouth, constipation, heat stroke, urinary retention and other adverse effects.

Some drugs interfere with absorption of prochlorperazine:

- anti-Parkinson drugs
- lithium
- Gastro-intestinal agents that are not absorbed (magnesium, aluminium and calcium salts, oxides and hydroxides): Reduced gastro-intestinal absorption of phenothiazine neuroleptics may occur. Such gastro-intestinal agents should not be taken at the same time as prochlorperazine.

High doses of prochlorperazine reduce the response to hypoglycaemic agents, the dosage of which might have to be raised.

The hypotensive effect of most antihypertensive drugs especially alpha adrenoceptor blocking agents may be exaggerated by prochlorperazine.

The action of some drugs may be opposed by prochlorperazine; these include amfetamine, levodopa, clonidine, guanethidine, adrenaline.

Increases or decreases in the plasma concentrations of a number of drugs, e.g. propranolol, phenobarbital have been observed.

There is an increased risk of agranulocytosis when prochlorperazine is used concurrently with drugs with myelosuppressive potential, such as carbamazepine or certain antibiotics and cytotoxics.

In patients treated concurrently with prochlorperazine and lithium, there have been rare reports of neurotoxicity.

Cytochrome P450 2D6 Metabolism:

Some phenothiazines are moderate inhibitors of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co-administration of prochlorperazine 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.

Stemzine should be avoided in patients taking monamine oxidase inhibitors (MAOI's). If Stemzine use is required, MAOI's should be ceased at least 14 days prior to Stemzine commencement.

Because of convulsive risk, the combined use of medicinal products which lower the seizure threshold should be carefully assessed.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

(Category C)

The use of Stemzine is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the potential benefits outweigh the potential risks.

Data from epidemiological studies cannot exclude the risk of congenital malformations in children exposed in utero to Stemzine.

Neuroleptics may occasionally prolong labour and at such time should be withheld until the cervix is dilated 3-4 cm.

When given in high doses during late pregnancy, phenothiazines have caused jaundice, hyperreflexia, hyporeflexia or prolonged extrapyramidal and neurological 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. Possible adverse effects on the foetus include lethargy or paradoxical hyperexcitability, tremor and a low Apgar score.

Use in lactation

Phenothiazines may be excreted in milk, therefore, breastfeeding is not recommended during treatment with Stemzine.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be warned about drowsiness and advised not to drive or operate machinery, particularly during the early days of treatment, until they know how Stemzine affects them.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

<u>Vascular disorders</u>

More common: Orthostatic hypotension. Elderly or volume depleted patients are particularly susceptible; it is more likely to occur after intramuscular injection.

Not known: Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs (see Section 4.4 Special warnings and precautions for use).

Blood and lymphatic system disorders

Not known: Eosinophilia.

Less common: Agranulocytosis, atypical lymphocytes, thrombocytopenia, leucopenia, aplastic anaemia.

Biochemical abnormalities

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

Cardiac disorders

Peripheral oedema, cardiac arrhythmias, ECG changes, QT interval prolongation, ST depression, U-Wave and T-Wave changes. Cardiac arrhythmias, including ventricular arrhythmias and atrial arrhythmias, atrioventricular block, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest have been reported during phenothiazine therapy possibly related to dosage.

Pre-existing cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose patients to cardiac events. There have been reports of sudden death, with possible causes of cardiac origin (see Section 4.4 Special warnings and precautions for use), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Not known: Torsade de pointes.

Skin and subcutaneous tissue disorders

Less common: Dermatitis allergic, maculopapular eruptions, erythema multiforme, urticaria, photosensitivity reaction, pigmentation disorder.

Less common: Contact skin sensitisation may occur rarely in those frequently handling preparations of certain phenothiazines (see Section 4.4 Special warnings and precautions for use).

Endocrine disorders

Less common: Endocrine disturbances including elevated prolactin levels, hyperglycaemia, intolerance to glucose, hypoglycaemia, menstrual irregularities, galactorrhoea, gynaecomastia, amenorrhoea, erectile dysfunction.

Not known: Temperature regulation disorder.

Gastrointestinal

More common: Constipation, dry mouth.

Less common: Paralytic ileus.

Genitourinary Renal and urinary disorders

Less common: Urinary retention.

Hepatobiliary disorders

Less common: Jaundice cholestatic, liver damage.

Nervous system disorders

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

Less common: Dystonia or dyskinesias, including oculogyric crisis usually transitory are commoner in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases.

Less common: Tardive dyskinesia: If this occurs it is usually, but not necessarily, after prolonged or high dosage. It can even occur after treatment has been stopped. Dosage should therefore be kept low whenever possible.

Less common: Torticollis and opisthotonus and trismus, seizures, EEG changes, headache, insomnia, catatonia, hyperpyrexia, agitation, dizziness.

Less common: Seizures have been reported.

Not known: Anticholinergic effects such as ileus paralytic, risk of urinary retention, dry mouth, constipation, accommodation disorder.

Not Known: Extrapyramidal syndrome:

- Akinesia with or without hypertonia, partially relieved by anticholinergic antiparkinsonian agents.

- Hyperkinetic-hypertonic movements, motor excitation.

- Akathisia.

Not Known: Insomnia.

Not Known: Convulsions.

Not Known: Dizziness.

Not Known: Sedation or somnolence.

Not Known: Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) may occur with any neuroleptic (see Section 4.4 Special warnings and precautions for use).

Eye Disorders

More common: Blurred vision.

Less common: Pigmentary retinopathy.

Less common: Corneal Deposits (brownish deposits in the anterior segment of the eye, due to accumulation of the drug and generally without effect on vision).

Not known: Accommodation disorder

Ocular changes and the development of metallic greyish-mauve coloration of exposed skin have been noted in some individuals mainly females, who have received chlorpromazine continuously for long periods (four to eight years). This could possibly happen with Stemzine.

Psychiatric disorders

Less common: Activation of psychotic symptoms.

Not known: Agitation, confusional state, delirium, anxiety.

Respiratory, thoracic and mediastinal disorders

Less common: Respiratory depression, nasal congestion.

Metabolism and Nutrition Disorders

Less common: Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have also been reported.

In post-marketing surveillance cases of hyperglycaemia or intolerance to glucose have been reported with antipsychotic phenothiazines (see Section 4.4 Special warnings and precautions for use).

Immune system disorders

Less common: Type 1 hypersensitivity reactions such as angioedema and urticaria have been reported.

Less common: Anaphylactic reaction.

Reproductive system and breast disorders

Less common: priapism, ejaculation disorder

Pregnancy, puerperium and perinatal conditions

Drug withdrawal syndrome neonatal (see Section 4.6 Fertility, pregnancy and lactation, Use in pregnancy).

Investigations

Not known: Weight increased, liver function test abnormal.

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 Section 4.9 Overdose. Also, long-term phenothiazine therapy has been associated with ECG changes and life threatening cardiac arrhythmias.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia).

4.9 OVERDOSE

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.

High doses cause depression of the central nervous system, presenting as lethargy, dysartria, ataxia, stupor, reduction in consciousness into coma, convulsions; mydriasis; cardiovascular symptoms (related to risk of QT interval prolongation), such as hypotension, ventricular tachycardia and arrhythmia; respiratory depression; hypothermia. These effects may be potentiated by other medicines or by alcohol. Anticholinergic syndrome may occur. Extremely serious parkinsonian syndrome may occur.

Treatment

In the event of overdose of Stemzine, take all appropriate measures immediately.

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).

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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Mechanism of action

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. α-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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

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.

Absorption

Prochlorperazine is well absorbed from the GI tract in rats but absorption is slowed in repeatedly treated animals.

Distribution

The drug is widely distributed to tissues including the brain, fat, kidney, heart and skin and is stored in reticuloendothelial tissues.

Metabolism

Phenothiazines are metabolised primarily in the liver and are subject to enterohepatic circulation.

Excretion

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- calcium hydrogen phosphate dihydrate
- magnesium stearate
- sodium lauryl sulfate
- wheat starch

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from Light.

6.5 NATURE AND CONTENTS OF CONTAINER

Stemzine tablets are available in blister packs of 25 and 100♦ tablets.

♦ Not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

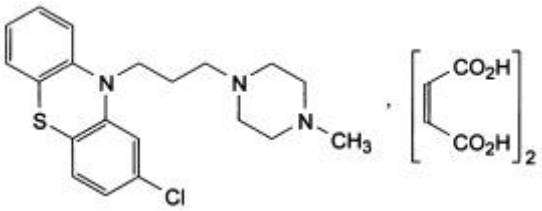
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Prochlorperazine maleate contains 62% of the active base. It is an odourless, nonhydroscopic, white or almost white, fine granular powder, which becomes coloured on exposure to light. It is very slightly soluble in water (less than 0.1% at 20º) and in alcohol, practically insoluble in ether.

Chemical structure

Prochlorperazine is 2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine. The chemical structure of prochlorperazine maleate is as follows:



Molecular Formula: $C_{20}H_{24}ClN_3S.2C_4H_4O_4$

CAS number

84-02-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

sanofi-aventis australia pty ltd

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Macquarie Park NSW 2113

Toll Free Number (medical information): 1800 818 806

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

21 October 1999

10 DATE OF REVISION

04 October 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Addition of cross reference and update to recommendations in "Children" subsection,
4.3	Update to contraindication for children and central nervous system depression.
4.4	Update to stroke warning. Reference to children relocated to "Paediatric use". Addition of cross references and warnings to "Paediatric use". Editorial change.
4.5	Desferrioxamine interaction details relocated to "Contraindicated combinations". Additional details provided for the interaction of monamine oxidase inhibitors with prochlorperazine.
4.6	Addition of warning that Neuroleptics may occasionally prolong labour.
4.8	Update to Adverse Effects relating to the Nervous system, immune system, vascular disorders, skin and subcutaneous tissue disorders, eye disorders and metabolism and nutrition disorders. Editorial changes.