PRODUCT INFORMATION

NAUSETIL
(Schedule 3 - prochlorperazine maleate)

NAME OF THE MEDICINE

NAUSETIL (prochlorperazine maleate).

Chemical name: 2-chloro-10-[3-(4-methylpiperazin-1-yl)propyl]-10\(\text{H}\)-phenothiazine bis[hydrogen (Z)-butenedioate].

Structural formula:

![Structural formula of NAUSETIL](image)

Chemical formula: C\(20\)H\(24\)ClN\(3\)S, 2C\(4\)H\(4\)O\(4\)
Molecular weight: 606.2
CAS: 84-02-6

DESCRIPTION

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

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.

Each NAUSETIL tablet contains 5 mg of prochlorperazine maleate as the active ingredient. Excipients include starch–wheat, magnesium stearate, sodium lauryl sulfate, calcium hydrogen phosphate anhydrous and quinoline yellow.

PHARMACOLOGY

As with other phenothiazines, prochlorperazine has actions on several neurotransmitter systems as follows:
• Antidopamine action, which probably contributes to both the therapeutic effect and unwanted effects including extrapyramidal disorders and endocrine disturbances.
• alpha-Adrenoreceptor antagonism, which contributes to cardiovascular side effects, e.g. orthostatic hypotension and reflex tachycardia.
• Potentiation of noradrenaline by blocking its reuptake into nerve terminals.
• Weak anticholinergic action.
• Weak antihistamine action.
• 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 gastrointestinal (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 (approximately 0.1%) of prochlorperazine and its metabolites is excreted in the first 24 hours in the urine and the drug may continue to be excreted in the urine for up to three weeks after cessation of long-term therapy. The elimination half-life is approximately 24 hours, presumably due to its enterohepatic circulation.

**INDICATIONS**

For the treatment of nausea associated with migraine.

**CONTRAINDICATIONS**

Circulatory collapse, central nervous system (CNS) 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**

NAUSETIL should be avoided in patients with renal dysfunction, Parkinson's disease, hypothyroidism, phaeochromocytoma, myasthenia gravis, prostatic hypertrophy.

**Hypotension** - The autonomic side effects of the piperazine derivatives are less troublesome than those of other phenothiazines, however care should be taken if NAUSETIL 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 five 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, e.g. intestinal obstruction and brain tumour. Reye's syndrome. The extrapyramidal symptoms which can occur secondary to chlorpromazine 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 chlorpromazine 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). The management of neuroleptic malignant syndrome should include immediate discontinuation of antipsychotic drugs, intensive monitoring and treatment of symptoms and treatment of any associated medical problems.

**QT intervals** - 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 torsades de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalaemia 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. NAUSETIL should, therefore, be used with caution in patients with stroke risk factors.

**Impaired hepatic function** - 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.

**Thromboembolism** – Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, NAUSETIL 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 NAUSETIL. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on NAUSETIL, should get appropriate glycaemic monitoring during treatment (see ADVERSE EFFECTS).

**Use in pregnancy** (Category C)

When given in high doses during late pregnancy, phenothiazines have caused jaundice, hyper-reflexia, hyporeflexia or prolonged extrapyramidal disturbances in the child. There is inadequate evidence of the safety of NAUSETIL in human pregnancy, but it has been widely used for many
years without apparent ill consequence. There is evidence of harmful effects in animals. Like other drugs it should be avoided in pregnancy unless the doctor considers it essential.

Neuroleptics may occasionally prolong labour, and at such a time should be withheld until the cervix is dilated 3 to 4 cm. Possible adverse effects on the fetus 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 nor whether it has a harmful effect on the newborn infant. Therefore, NAUSETIL is not recommended for breastfeeding mothers unless the expected benefits outweigh any potential risk.

**Use in children**

NAUSETIL is not recommended for use in children under 10 kg or aged under 2 years, as acute extrapyramidal reactions are more likely to occur.

**Effect on ability to drive or operate machinery**

See PRECAUTIONS section, Sedative effect.

**Interactions with other drugs**

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, sulfotride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparflaxacin.
- 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.

Simultaneous administration of desferrioxamine and prochlorperazine has been observed to induce a transient metabolic encephalopathy characterised by loss of consciousness for 48 to 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. Antihypertensive 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 and 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, electrocardiographic (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.

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

Endocrine - Endocrine disturbances including elevated prolactin levels, hyperglycaemia, 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, seizures, electroencephalographic (EEG) changes, headache, insomnia, catatonia, hyperpyrexia

Ocular - Pigmentary retinopathy

Psychiatric - Activation of psychotic symptoms

Respiratory - Respiratory depression.

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

Severe 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**

**Adults**
The recommended dosage is 5 or 10 mg two or three times daily.
For acute treatment, 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 NAUSETIL for a child, the dosage is 250 microgram/kg bodyweight two or three times a day. NAUSETIL has been associated with dystonic reactions particularly after a cumulative dosage of 500 microgram/kg. It should, therefore, be used cautiously in children. NAUSETIL is not recommended for children weighing less than 10 kg.

**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 humans.

**Treatment**
Acute dystonic reactions - Intramuscular benztropine (or another antiparkinsonian agent) should be given immediately (adults: 1 to 2 mg intramuscularly; children: 0.2 mg intramuscularly initially, with increments if necessary).

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 extrapyramidal side effects increase the risk of pulmonary aspiration should vomiting occur. Gastric lavage may be useful even several hours after the drug has been ingested since prochlorperazine reduces gastric motility. 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.

Contact the Poisons Information Centre on 131126 for management of overdose.

**PRESENTATION**
NAUSETIL 5 mg tablets are round, biconvex and pale yellow engraved with “M” on one side and plain on the other: Available in packs of 10 tablets.

**STORAGE**
Store below 30°C. Protect from light.

**POISONS SCHEDULE**
S3 (Pharmacist Only Medicine) – 10 tablet pack
SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos St
St Leonards NSW 2065
Australia

DATE OF TGA APPROVAL

Approved by the Therapeutic Goods Administration: 16 October 2009
Date of most recent amendment: 25 May 2010.