NEW ZEALAND DATA SHEET

ANTINAUS

1. Product Name

ANTINAUS 5 mg tablets.

2. Qualitative and Quantitative Composition

Each ANTINAUS tablet contains 5 mg of prochlorperazine maleate.

ANTINAUS contains lactose. For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

White biconvex tablets, 9/32" (7.1mm) diameter, imprinted PM/5 on one side.

The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

ANTINAUS is used in vertigo due to Meniere's syndrome, labyrinthitis and other causes, and for nausea and vomiting from whatever cause. It may also be used for migraine, schizophrenia (particularly in the chronic stage), acute mania and as an adjunct to the short term management of anxiety.

For the treatment of nausea associated with migraine. (This indication only is classified Pharmacist Only).

4.2 Dose and method of administration

Dose

Nausea and vomiting

Adults

Prevention of nausea and vomiting: 5 or 10 mg two or three times daily.

Treatment of nausea and vomiting: 20 mg immediately followed, if necessary, by 10 mg two hours later.

Children

Prevention and treatment of nausea and vomiting: if it is considered unavoidable to use prochlorperazine for a child, the dosage is 0.25 mg/kg bodyweight, two or three times a day.

Vertigo and Meniere's disease

Adults

5 mg three times a day, increasing if necessary to a total of 30 mg daily. After several weeks dosage may be reduced gradually to 5-10 mg daily.

Adjunct in the short-term management of anxiety

Adults

10-20 mg daily in divided doses initially but this may be increased if necessary to a maximum of 40 mg daily in divided doses.

Schizophrenia and other psychotic disorders

Adults

Usual effective daily oral dosage is in the order of 75-100 mg daily. Patients vary widely in response. The following schedule is suggested:

Initially 12.5 mg twice daily for 7 days, the daily amount being subsequently increased by 12.5 mg at four to seven day intervals until a satisfactory response is obtained. After some weeks at the effective dosage, an attempt should be made to reduce this dosage. Total daily amounts as small as 50 mg or even 25 mg have sometimes been found to be effective.

Children

Prochlorperazine is not recommended for children weighing less than 10 kg.

Elderly

Prochlorperazine should be used cautiously in this group in psychotic disorders. Elderly patients susceptible to centrally acting medicines hence lower initial dosage is recommended. There is an increased risk of drug-induced Parkinsonism in the elderly, particularly after prolonged use. Correct initial diagnosis of the disorder is important. Care should also be taken not to confuse adverse effects of prochlorperazine, e.g. orthostatic hypotension with effects due to the primary disorder.

4.3 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.

4.4 Special warnings and precautions for use

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, 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 section 4.8).

Cerebrovascular events: An increased risk of cerebrovascular events has been reported in elderly patients with dementia treated with atypical antipsychotic drugs. The mechanism of such risk increase is not known. 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 section 4.8).

Elderly patients with dementia-related psychosis: 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. 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).

Hyperglycaemia: hyperglycemia 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 section 4.8).

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.

4.5 Interaction with other medicines and other forms of interaction

Caution is required with the use of the following medicines due to the risk of QT prolongation (see section 4.4):

- 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.

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.

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; dose adjustments of the anticonvulsants may be necessary.

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.

4.6 Fertility, pregnancy and lactation

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 medicines such as psychotropic or antimuscarinic medicines were co-administered;
- 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 prochlorperazine 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.

Breast-feeding

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

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable 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 section 4.4), 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 section 4.4).

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, EEG changes, headache, insomnia, catatonia, hyperpyrexia. Cases of convulsions have been reported.

Ocular: pigmentary rentinopathy.

Psychiatric: activation of psychotic symptoms.

Respiratory: respiratory depression.

Metabolic 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 section 4.4).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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.

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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotic, ATC code: N05AB04

Mechanism of action

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.

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.

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.

Biotransformation

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

Elimination

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.

6. Pharmaceutical Particulars

6.1 List of excipients

Lactose, maize starch, povidone, microcrystalline cellulose, magnesium stearate and ethanol.

ANTINAUS is gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Blister packs of 10, 100 and 500 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Pharmacist Only Medicine (only for the treatment of nausea associated with migraine): blister packs of 10 tablets.

Prescription Medicine: blister packs of 100 and 500 tablets.

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

Pharmacist Only Medicine: 13 January 2005

Prescription Medicine: 15 May 1975

10. Date of Revision of the Text

19 May 2017	Revised to SmPC format. Safety update to section 4.5.