NEULACTIL
PRODUCT INFORMATION

NAME OF THE MEDICINE
Periciazine

DESCRIPTION
Periciazine is 2 -cyano - 10 - 3' - (4 - hydroxpiperidino-propyl) phenothiazine.

Periciazine is a yellow crystalline powder, almost without odour, non-hygroscopic and sensitive to light. It melts at about 115°C. The molecular weight is 365.48. It is insoluble in water, slightly soluble in ether, fairly soluble in ethanol, acetone and benzene and freely soluble in chloroform.

Neulactil tablets contain periciazine (2.5 mg and 10 mg) and the following excipients: microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal anhydrous silica and wheat starch.

PHARMACOLOGY

Actions and Pharmacokinetics

Periciazine is a phenothiazine with a piperidine side chain. It has similar antipsychotic action to other phenothiazines but produces more sedation. It also has adrenolytic, anticholinergic and extrapyramidal effects.

Periciazine is well absorbed after oral administration. However, like other phenothiazines, periciazine appears to be subject to extensive first pass metabolism in the gut and/or liver with low plasma levels of parent compound.

A group of 12 healthy human volunteers were administered two 10mg periciazine capsules. A peak concentration of 150 ng/ml (410 nmol/l) was achieved 2 hours after drug administration and the half-life was approximately 12 hours. In some subjects, detectable amounts of periciazine were still present in the blood after 36 hours. There is high inter-patient variability.

The majority of the product undergoes conjugation in the liver and is excreted in the urine.

As with other phenothiazines, high inter-patient variability is to be expected.

INDICATIONS
Severe anxiety and tension states and the maintenance treatment of the psychotic patient. It is useful in controlling such symptoms as impulsiveness and aggression.

CONTRAINDICATIONS
Periciazine should never be used in the following circumstances:

Circulatory collapse.

Acute intoxication with central depression and coma.

Previous history of blood dyscrasias. or agranulocytosis.

Hypersensitivity to phenothiazines or to any of the excipients contained in the tablets.

Hypersensitivity or intolerance to gluten, because the medicinal product contains wheat starch (gluten).

Risk of angle-closure glaucoma.

Risk of urinary retention due to urethroprostatic disorders.

Periciazine should not be administered in association with spinal or regional anaesthetics.

Periciazine should not be used in patients with convulsive disorders that are not receiving appropriate anticonvulsive medication.

Periciazine is contraindicated in children younger than 1 year, due to a possible link between use of phenothiazine-containing products and Sudden Infant Death Syndrome (SIDS).

Periciazine is contraindicated in combination with dopaminergic antiparkinsonism agents (see **INTERACTIONS WITH OTHER MEDICINES**).

Neuroleptics should be avoided in patients with phaeochromocytoma or liver dysfunction.

PRECAUTIONS

WARNING: Periciazine may cause a mild leukopenia or agranulocytosis in some patients.

When Neulactil is prescribed in conjunction with other centrally acting drugs, the usual dose of these compounds should be reduced by at least half while the new treatment is being introduced. Caution should be exercised when Neulactil is prescribed with other phenothiazine derivatives or CNS depressants such as barbiturates, analgesics, narcotics or antihistamines as it may potentiate their effects.

Activities such as the control of vehicles or machinery should not be undertaken until it is evident that any soporific effect has subsided. Patients should be warned about drowsiness, slowing of reaction time and impaired judgement.

Neuroleptics should be avoided in patients with renal dysfunction, epilepsy, Parkinson's disease, hypothyroidism, cardiac failure and myasthenia gravis. As periciazine has an anticholinergic action, it should be avoided in patients who have a history of prostatic hypertrophy.

Patients should be strongly advised against ingesting alcohol or any medication containing alcohol while under treatment.

Patients with the following diseases/disorders should be monitored closely during treatment: Cardiovascular disorders, bradychardia, hypokalemia or familial history of prolongation of QT because of a risk of worsening of long QT-syndrome, which may also elevate the risk for developing torsade de pointes, tachycardia and sudden death. As with other neuroleptics, cases of QT interval prolongation have been reported with periciazine. 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 (e.g. ECG and serum potassium) and control of blood pressure 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**).

Caution should be taken in patients with cardiovascular disease or family history of QT prolongation. Concomitant use with QT prolonging drugs should be avoided.

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. Periciazine should therefore be used with caution in patients with stroke risk factors.

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

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

It is essential that periciazine treatment should be discontinued in the event of unexplained fever as this may be one of the signs of the neuroleptic malignant syndrome described with neuroleptics, the clinical manifestations of which include pallor, hyperthermia, autonomic disturbances, altered consciousness and muscle rigidity. Signs of autonomic dysfunction such as sweating and arterial instability may precede the occurrence of hyperthermia and thus constitute early presenting signs. Certain risk factors such as dehydration or organic brain damage appear to be predisposing factors.

Use with caution in patients with certain cardiovascular conditions, because of the quinidine-like, tachycardia-inducing and hypotensive effects of this class of products.

Careful monitoring of treatment with periciazine is required in epileptics due to a possible lowering of the seizure threshold. The occurrence of convulsive seizures necessitates the discontinuation of periciazine treatment. Periciazine should not be used in patients with convulsive disorders that are not receiving appropriate anticonvulsive medication (see **CONTRAINDICATIONS**).

Careful monitoring of treatment with periciazine is required in patients with severe hepatic impairment and/or renal impairment, due to the risk of accumulation.

Because of the risk of photosensitisation, patients should be advised to avoid exposure to direct sunlight.

Apart from exceptional situations, periciazine should not be used in patients with Parkinson's disease. In such patients, careful monitoring is required and caution should be exercised if constipation develops. The onset of paralytic ileus, which can manifest itself as abdominal bloating and pain, requires emergency treatment.

Driving a Vehicle or Performing Other Hazardous Tasks

Patients, and especially those who drive or operate machines, should be informed of the risk of somnolence associated with this medication, particularly at the beginning of treatment.

Paediatric Use

- Use in children < 1 year of age – contraindicated (see **CONTRAINDICATIONS**).
- Use in children 1-3 years of age – not recommended.
- Use in children 3-6 years of age is reserved for exceptional situations in specialist units. When it is prescribed in this population, neurological signs or symptoms should be carefully monitored. It is advisable to perform an annual clinical examination to evaluate learning abilities in children, due to the cognitive impact, and dosage should be regularly adapted depending on the child's clinical condition.

Use in the Elderly

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.

Paralytic ileus has occurred in patients, particularly in the elderly, taking one or more drugs with anticholinergic action for extended periods.

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

The elderly are particularly susceptible to postural hypotension, careful monitoring is required.

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

Use in Pregnancy (Category C)

Safety in pregnancy and lactation has not been established. Neonates exposed to antipsychotic drugs (including periciazine) during the third trimester of pregnancy are at risk of experiencing extrapyramidial neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of neurological disorders such as extrapyramidal symptoms including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limiting, in other cases neonates have required additional medical treatment or monitoring.

The following effects have also 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;

Appropriate monitoring and treatment of neonate born to mother receiving periciazine are recommended.

Periciazine should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Precaution is needed when both neuroleptics and antiparkinsonian agents are used together towards the end of pregnancy, due to their additive atropine - like effects.

A period of monitoring of the neurological and gastro-intestinal functions of the neonate appears warranted.

Use in Lactation

Safety in lactation has not been established. In the absence of data on excretion in breast milk, breastfeeding is not recommended during treatment.

INTERACTIONS WITH OTHER MEDICINES

The use of dopaminergic antiparkinsonism agonist agents with periciazine is contraindicated due to reciprocal antagonism between the dopaminergic agonist and neuroleptics (see **CONTRAINDICATIONS**).

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, lithium.
- 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, tetracosactides (tetracosactrins).
- Other antipsychotics.

Lithium can increase the risk of the appearance of neuropsychiatric signs suggestive of neuroleptic malignant syndrome or lithium poisoning. Regular clinical and biological monitoring of serum (lithium) should be performed, especially when the combination is initiated.

Intensification of the sedative effects of neuroleptics may be intensified by alcohol. Impaired vigilance may make it dangerous to drive or use machines. Avoid consumption of alcoholic beverages and medications containing alcohol while being treated with periciazine.

The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol, other sedatives, and other central nervous system depressants: morphine derivatives, barbiturates, benzodiazepines,anxiolytics other than benzodiazepines, hypnotics, sedative antidepressants, sedative H1 antihistamines, central antihypertensives, baclofen, thalidomide. Enhanced central depression and respiratory depression may occur. Impaired vigilance may make it dangerous to drive or use machines.

Phenothiazines, such as periciazine, are potent inhibitors of CYP2D6. Therefore 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.

The hypotensive effect and the risk of postural hypotension of most antihypertensive drugs especially alpha adrenoceptor blocking agents may be exaggerated by neuroleptics.

The mild anticholinergic effect of neuroleptics may be enhanced by other anticholinergic drugs possibly leading to constipation, heat stroke, etc.

The action of some drugs may be opposed by neuroleptics; these include amphetamine, levodopa, clonidine, guanethidine, adrenaline (epinephrine).

Adrenaline must not be used in patients overdosed with neuroleptics.

Anticholinergic agents may reduce the antipsychotic effect of neuroleptics.

Some drugs interfere with absorption of neuroleptic agents: topical gastro-intestinal agents (e.g. antacids), antiparkinsonian agents, lithium. Antacids should not be taken at the same time as phenothiazine neuroleptics. Increases or decreases in the plasma concentrations of a number of drugs, e.g. propranolol, phenobarbital (phenobarbitone) have been observed but were not of clinical significance.

High doses of neuroleptics may reduce the response to hypoglycaemic agents the dosage of which might have been raised.

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

It is possible that this may occur with periciazine since it shares many of the pharmacological activities of prochlorperazine.

Atropine and other atropine-like substances (e.g. imipramine antidepressants, sedative H1 antihistamines, anticholinergic antiparkinsonian agents, atropine-like antispasmodics, disopyramide) in combination with periciazine may increase cumulative side effects such as urinary retention, constipation and dry mouth (i.e. atropine-like side effects).

ADVERSE EFFECTS

Behavioural

At the start of treatment, some drowsiness is not uncommon but this effect usually wears off within a few days. Adjustment of dosage, e.g. by giving the larger portion in the evening, will invariably lessen the effect, but care should be exercised when barbiturates or other sedatives are prescribed with periciazine, particularly for children or elderly patients.

Impaired psychomotor activity is a frequent initial untoward reaction. If a toxic-confusional state appears, the medication should be stopped immediately.

Paradoxical effects, such as agitation, insomnia, inversion of sleep, increased aggressiveness and activation of psychotic symptoms, have been occasionally observed.

Indifference, anxiety reactions and mood variations have been reported.

Hepatic

Jaundice, occurs in a very small percentage of patients taking neuroleptics. A premonitory sign may be a sudden onset of fever after one to three weeks of treatment followed by the development of jaundice. Neuroleptic jaundice has the biochemical and other characteristics of obstructive jaundice and is associated with obstruction of the canaliculi by bile thrombi; the frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Treatment should be withheld on the development of jaundice.

Cholestatic jaundice and liver injury, mainly of cholestatic or mixed type, are very rarely reported in patients treated with periciazine.

Cardiovascular

Hypotension, usually postural, commonly occurs. Elderly or volume depleted subjects are particularly susceptible. These reactions occur more often at the beginning of treatment or when initial high dosages are used.

Cardiac arrhythmias, including atrial arrhythmia, A-V block, ventricular tachycardia and fibrillation have been reported during neuroleptic therapy, possibly related to dosage. Pre-existing cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose. ECG changes, usually benign, include ST depression, U-waves and T-wave changes. QT interval prolongation has been reported.

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**).

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.

Gastrointestinal

Vomiting, nausea, constipation, faecal impactation, diarrhoea and paralytic ileus may occur.

Respiratory

Respiratory depression is possible in susceptible patients.

Haematological

A mild leukopaenia occurs in up to 30% of patients on prolonged high dosage of neuroleptics. Agranulocytosis may occur rarely; it is not dose related. These may occur suddenly or follow a fall in blood count usually during the first 2 or 3 months of treatment. The occurrence of unexplained infections or fever requires immediate haematological investigation.

Positive serology for anti-nuclear antibodies without clinical lupus erythematosus has been reported.

Nervous system

Early dyskinesia has been reported.

Extrapyramidal: Acute dystonias or dyskinesias, usually transitory are commoner in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases.; akinesia with or without hypertonia, hyperkinetic -hypertonic movements, motor excitation, akathisia,

Parkinsonism is more common in adults and the elderly. It usually develops after weeks or months of treatment. One or more of the following may be seen: tremor, rigidity, akinesia or other features of Parkinsonism.

Commonly just tremor.

Sedation or somnolence, anticholinergic effects such as dry mouth, constipation, paralytic ileus (see **PRECAUTIONS**), accommodation disorders, risk of urinary retention have been reported.

Skin and eyes

Contact skin sensation is a serious but rare complication in those frequently handling preparations of phenothiazines; the greatest care must be taken to avoid contact of the drug with the skin. Allergic skin reactions, e.g. skin rashes of various kinds, may also be seen in patients treated with drug. Patients should be warned that they may develop photosensitivity in sunny weather and should avoid exposure to direct sunlight and that retinal changes may occur.

In some patients blurred vision and aggravation of glaucoma have been reported. Abnormal pigmentation, including deposits in the anterior segment of the eye, due to accumulation of the product, have been observed, usually when high doses of phenothiazines are given for prolonged periods.

Endocrine

Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea; frigidity, impotence. Other effects include delayed ovulation, menstrual irregularities, lactation, gynaecomastia, changes in libido, inhibition of ejaculation, false positive pregnancy tests, weight gain and oedemas, have been known to occur. Increased appetite and weight gain have been reported in some patients on periciazine therapy.

Tardive Dyskinesia

Tardive Dyskinesia may appear in some patients on long term therapy or may appear after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterised by rhythmical involuntary movement of tongue, face, mouth or jaw (e.g. protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

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. Anti-parkinsonian agents usually do not alleviate symptoms. It is suggested that anti-psychotic 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 anti-psychotic drugs. The syndrome is characterised by muscular rigidity, fever, hyperthermia, altered consciousness and autonomic instability (eg 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.

Allergic and Toxic Reactions

Asthma, laryngeal oedema, angioneurotic oedema, hyperpyrexia and other allergic reactions may also occur.

Other

Nasal stuffiness, dry mouth (sometimes with oral infections and dental caries), perspiration and changes in body temperature.

Pregnancy, puerperium and perinatal conditions

Neonatal abstinence syndrome has been reported.

Miscellaneous

Phenothiazine therapy, historically, has been associated with hypostatic pneumonia and unexpected sudden deaths with possible causes of cardiac origin. The reports of unexpected sudden death with periciazine are very rare. The physician should also be alerted to the possible development of “silent pneumonias” with phenothiazine therapy.

Priapism has been very rarely reported in patients treated with periciazine.

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

DOSAGE AND ADMINISTRATION

In all cases, dosage may be progressively increased until the most effective level is reached after which the dosage should be adjusted to maintain control of symptoms.

Mild to Moderate Conditions in General Practice

Adults

The initial daily dosage is 15 to 30 mg divided into two portions with the larger dose given in the evening.

Geriatric Patients

The starting dose is 10 mg/day, increasing according to therapeutic effect and patient tolerance, to a maximum of about 30 mg daily in divided doses.

Moderate to Severe Conditions

Hospitalised Adult Patients

Initial dosage is 25 to 75 mg/day orally, administered in divided doses.

Children

The initial daily dosage should not exceed 0.5 mg per year of age. Use in children below 1 year of age is contraindicated. In older children (16 years) the twenty four hour dose should be about 1 mg/year of age. Dosages up to 75 mg/day are used in hospitals without any untoward effects.

OVERDOSAGE

Symptoms

The symptoms of overdosage with phenothiazines include CNS depression presenting as lethargy, dysartria, ataxia, stupor; progressing from drowsiness to coma with areflexia, patients with early or mild intoxication may experience restlessness, confusion, agitation,

excitement or a delirious state. Other symptoms include cardiovascular symptoms (related to QT interval prolongation), such as hypotension, tachycardia, arrhythmias, ECG changes; respiratory depression, hypothermia, pupillary dilation or constriction, tremor, muscle twitching, spasm or rigidity, convulsions, arrhythmias and hypotension, dystonic movements, muscular hypotonia, difficulty in swallowing and breathing, cardiovascular collapse, cyanosis and respiratory and/or vasomotor collapse, possibly with sudden apnoea. Polyuria has also been noted which may result in dehydration. Severe extra-pyramidal dyskinesias may occur.

These effects may be potentiated by other medicines or by alcohol. Anticholinergic syndrome is of importance. Extremely serious parkinsonian syndrome may occur.

Acute toxicity has been determined in animals. LD 50 values range from 44 mg/kg (intravenous, mouse) to 530 mg/kg (oral mouse).

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

Treatment

The stomach should be emptied by aspiration and lavage. Emetics should not be used, not only because the antiemetic action of phenothiazines 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.

To counter acute hypotension the patient should be placed in the head down position and noradrenaline or phenylephrine administered intravenously. Adrenaline is contraindicated.

The central nervous depression should generally be allowed to recover naturally, however artificial respiration may be required. Appropriate antibiotic therapy should be instituted for any respiratory infections.

Hypothermia should be allowed to recover naturally unless the temperature approached levels at which cardiac arrhythmias may be feared (e.g. 29.4°C). Shivering is a sign of the waning effects of the drug.

Severe extrapyramidal reactions should be treated with benztropine or another antiparkinsonian agent (intramuscular dose in adults: 1 to 2mg, children 0.2 to 0.25mg initially with increments if necessary).

PRESENTATION AND STORAGE CONDITIONS

Tablets, 2.5 mg (yellow, scored, marked NEULACTIL): 100s; 10 mg (yellow, scored, marked 10): 100s.
Store below 25°C. Protect from light.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

NAME AND ADDRESS OF THE SPONSOR

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

DATE OF FIRST INCLUSION IN THE ARTG

21 October 1991

DATE OF MOST RECENT AMENDMENT

25 August 2017