SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pericyazine 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pericyazine 10mg

3 PHARMACEUTICAL FORM

Pericyazine 10mg Tablets: Circular, very pale lime-yellow tablet, with one face impressed ‘S172’ and a break-line on reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

a) In adults with schizophrenia or other psychoses, for the treatment of symptoms or prevention of relapse.

b) In anxiety, psychomotor agitation, violent or dangerously impulsive behaviour. Pericyazine is used as an adjunct to the short-term management of these conditions.

4.2 Posology and method of administration

*Route of administration:* oral.

Dosage requirement varies with the individual and the severity of the condition being treated. Initial dosage should be low with progressive increases until the desired response is obtained, after which dosage should be adjusted to maintain control of the symptoms.

*Severe conditions*
Indication (a)

Adults: Initially 75 mg per day in divided doses. Dosage should be increased by 25 mg per day at weekly intervals until the optimum effect is achieved. Maintenance therapy would not normally be expected to exceed 300 mg per day.

Elderly: Initially 15-30 mg per day in divided doses. If this is well tolerated the dosage may be increased if necessary for optimum control of behaviour.

Mild or moderate conditions

Indication (b)

Adults: Initially 15-30 mg daily, divided into two portions with a larger dose being given in the evening.

Elderly: 5-10 mg per day is suggested as a starting dose. It may be divided so that a larger portion is given in the evening. Half or quarter the normal adult dose may be sufficient for maintenance therapy.

Pericyazine tablets are not recommended for children.

4.3 Contraindications

See use in pregnancy below. Known hypersensitivity to pericyazine or to any of the other ingredients.

4.4 Special warnings and precautions for use

Neuroleptics should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis, prostrate hypertrophy. It should be avoided in patients known to be hypersensitive to phenothiazines or with a history of narrow angle glaucoma or agranulocytosis. It should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper-hypothermia).

Close monitoring is required in patients with epilepsy or a history of seizures, as phenothiazines may lower the seizure threshold.

As agranulocytosis may occur rarely, regular monitoring of the complete blood count is recommended. It is imperative that 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 arterial 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.

The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see section 4.8 below), and requires immediate haematological investigation.

Acute withdrawal symptoms, including nausea, vomiting 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.

In schizophrenia, the response to neuroleptic treatment may be delayed. If treatment is withdrawn, the recurrence of symptoms may not become apparent for some time.

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. The risk-benefit should be fully assessed before pericyazine treatment is commenced. If the clinical situation permits, medical and laboratory evaluations (e.g. biochemical status and ECG) should be performed to rule out possible risk factors (e.g. cardiac disease; family history of QT prolongation; metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesaemia; starvation; alcohol abuse; concomitant therapy with other drugs known to prolong the QT interval) before initiating treatment withpericyazine and during the initial phase of treatment, or as deemed necessary during the treatment (see also sections 4.5 & 4.8).

Avoid concomitant treatment with other neuroleptics (see section 4.5).

Stroke: In randomised clinical trials versus placebo performed in a population of 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. Pericyazine should be used with caution in patients with stroke risk factors.

As with all antipsychotic drugs, Pericyazine 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.

Because of the risk of photosensitisation, patients should be advised to avoid exposure to direct sunlight.
In those frequently handling preparations of phenothiazines, the greatest care must be taken to avoid contact of the drug with the skin, since contact skin sensitisation occurs rarely.

Cases of venous thromboembolism (VTE) 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 pericyazine and preventive measures undertaken.

Hyperglycaemia or intolerance to glucose has been reported in patients with pericyazine.

Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on pericyazine, should get appropriate glycaemic monitoring during treatment (see section 4.8).

**Increased Mortality in Elderly people with Dementia**

Data from two large observational studies showed that elderly people with dementia who are treated with conventional (Typical) antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

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

### 4.5 Interaction with other medicinal products and other forms of interaction

**Interactions of phenothiazine neuroleptics:**

The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol, barbiturates and other sedatives. Respiratory depression may occur.

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

There is an increased risk of arrhythmias when neuroleptics are used with concomitant QT prolonging drugs (including certain antiarrhythmics, antidepressants, and other antipsychotics) and drugs causing electrolyte imbalance (see sections 4.4 and 4.8).

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 amfetamine, levodopa, clonidine, guanethidine, adrenaline.

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.

Anticholinergic agents may reduce the antipsychotic effect of neuroleptics.

Some drugs interfere with absorption of neuroleptic agents: antacids, anti-Parkinson drugs, lithium. Increases or decreases in the plasma concentrations of a number of drugs, e.g, propranolol, phenobarbital 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 to be raised.

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

Adrenaline must not be used in patients overdosed with neuroleptics.

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 this may occur with Pericyazine since it shares many of the pharmacological properties of prochlorperazine.

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

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

4.6 Fertility, pregnancy and lactation

There is inadequate evidence of the safety of pericyazine in human. There is evidence with some neuroleptics of harmful effects in animals. Like other drugs pericyazine should be avoided in pregnancy unless the physician considers it essential. It 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 low Apgar score.

Neonates exposed to antipsychotics (including pericyazine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
Phenothiazines may be excreted in milk, therefore breastfeeding should be suspended during treatment.

4.7 Effects on ability to drive and use machines

Patients should be warned about drowsiness during early days of treatment, and advised not to drive or operate machinery. The elderly are particularly susceptible to postural hypotension.

4.8 Undesirable effects

Liver function: 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 (cholestatic) 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. Liver injury has been reported very rarely in patients treated with pericyazine. Treatment should be withheld on the development of jaundice.

Cardiorespiratory: hypotension, usually postural, commonly occurs. Elderly or volume depleted subjects are particularly susceptible. ECG changes, include QT prolongation (as with other neuroleptics), ST depression, U-Wave and T-Wave changes. Cardiac arrhythmias, including ventricular arrhythmias and atrial arrhythmias, a-v block, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest have been reported during neuroleptic phenothiazine therapy, possibly related to dosage. Pre-existing cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose. There have been isolated reports of sudden death, with possible cases of cardiac origin (see section 4.4, above), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Respiratory depression is possible in susceptible patients. Blood picture: a mild leukopenia occurs in up to 30% of patients on prolonged high dosage of neuroleptics; agranulocytosis may occur rarely; it is not dose-related.

Extrapyramidal: acute dystonias or dyskinesias, usually transitory are commoner in children and young adults, and usually occur within the first four days of treatment or after dosage increases.
- Akathisia characteristically occurs after large initial doses.
• Parkinsonism is commoner 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.
• 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.

Skin and eyes: contact skin sensitisation may occur rarely in those frequently handling preparations of phenothiazines (see section 4.4, above. Skin rashes of various kinds may also be seen in patients treated with the drug. Patients on high dosage should be warned that they may develop photosensitivity in sunny weather and should avoid exposure to direct sunlight.

Endocrine: hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea; impotence.

Priapism has very rarely been reported in patients treated with pericyazine. Neuroleptic malignant syndrome (hyperthermia, rigidity autonomic dysfunction and altered consciousness) may occur with any neuroleptic.

Minor side effects are nasal stuffiness, dry mouth, insomnia, agitation

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs (see also section 4.4).

Intolerance to glucose, hyperglycaemia (see section 4.4).

Pregnancy, puerperium and perinatal conditions; drug withdrawal syndrome neonatal (see section 4.6) – Frequency not known.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

### 4.9 Overdose

**Toxicity and treatment of overdose**

Symptoms of neuroleptic overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, ECG changes, ventricular arrhythmias and hypothermia. Severe extra-pyramidal dyskinesias may occur.

If the patient is seen sufficiently soon (up to 6 hours) after ingestion of a toxic dose, gastric lavage may be attempted. Pharmacological induction of emesis is unlikely to
be of any use. Activated charcoal should be given. There is no specific antidote. Treatment is supportive.

Generalised vasodilatation may result in circulatory collapse; raising the patients legs may suffice, in severe cases, volume expansion by intravenous fluids may be needed; infusion fluids should be warmed before administration in order not to aggravate hypothermia.

Positive inotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstrictor agents are not generally recommended; avoid the use of adrenaline.

Ventricular or superaventricular tachy-arrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life threatening, appropriate antiarrhythmic therapy may be considered. Avoid lignocaine, and as far as possible long acting, anti-arrhythmic drugs.

Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine (5-10mg) or orphenedrine (20-40mg) administered intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam.

Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium may be tried.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pericyazine is a neuroleptic with cardiovascular and antihistamine effects similar to those of chlorpromazine, but it has a stronger antiserotonin effect and a powerful central sedative effect.

5.2 Pharmacokinetic properties

Kinetics: there is little information about plasma concentrations, distribution and excretion in humans. The rate of metabolism and excretion of phenothiazines decreases in old age.
5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous USP,
Microcrystalline cellulose (E460),
Sodium starch glycollate,
Magnesium stearate BP,
Colloidal silicon dioxide (E551),
Methyl hydroxybenzoate BP (E218)

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container

Securitainer or HDPE bottle containing 500 tablets.
PVDC coated UPVC aluminium foil blister containing 84 tablets.
6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

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