SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Prochlorperazine tablets BP 5mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5mg Prochlorperazine Maleate PhEur.

Excipients with known effect: Each 5mg tablet contains 61.00mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 Pharmaceutical Form
White to off-white, uncoated tablets.

White to off-white, circular, flat bevelled-edge uncoated tablets impressed “C” on one face and the identifying letters “Z and P” on either side of a central division line on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Prochlorperazine is a potent phenothiazine neuroleptic.

1. It is indicated in vertigo due to Meniere's syndrome, labyrinthitis and other causes, and for nausea and vomiting from any cause including that associated with migraine.
2. It may also be used for schizophrenia (especially in the chronic stage), acute mania and as an adjunct to the short term management of anxiety.

4.2 Posology and method of administration

Posology
Elderly: Use with caution in this age group in psychotic disorders. Owing to the susceptibility of elderly patients to centrally acting drugs, lower initial dosage is recommended. Care should be taken not to confuse adverse effects
of prochlorperazine (eg orthostatic hypotension) with effects due to the primary disorder.

Vertigo and Meniere's syndrome:
Adults: 5mg three times daily, increasing where necessary to a maximum of 30mg daily. After several weeks of therapy, dosage may be gradually reduced to 5-10mg daily.

Nausea and vomiting:
Adults: Prevention: 5-10mg two or three times daily. Treatment: 20mg immediately, followed by, if necessary, 10mg two hours later.

Adjunct to the short-term management of anxiety:
Adults: 15-20mg daily in divided doses, increasing where necessary to a maximum of 40mg daily in divided doses.

Schizophrenia and other psychotic disorders: Usually 75-100mg daily, but patients vary widely in response. The following dosage regime is suggested: Initially 12.5mg twice daily for seven days, rising by 12.5mg increments at four to seven day intervals until a satisfactory response is obtained. After some weeks at the effective dosage level, an attempt should be made to reduce the dosage. Total daily dosages as low as 50mg, or even 25mg, have sometimes found to be adequate.

Paediatric population: Not recommended for children under 12 years of age. To reduce side effects gradual withdrawal of treatment is advisable.

Method of Administration
For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Phaeochromocytoma.

4.4 Special warnings and precautions for use

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine, as it contains lactose.

- Prochlorperazine should be avoided in patients with liver or renal dysfunction, history of jaundice, Parkinson’s disease, hypothyroidism, cardiac failure, myasthenia gravis, prostate hypertrophy. It should be avoided in patients known to be hypersensitive to phenothiazine or with a history of narrow angle glaucoma or agranulocytosis.

- Close monitoring is required in patients with epilepsy or a history of seizures, as phenothiazines may lower the seizure threshold.
• 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 (see section 4.8) and requires immediate haematological investigation.

• 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.

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

• 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).

• Avoid concomitant neuroleptics.

• The elderly are particularly susceptible to postural hypotension. Use with caution in the elderly, especially during very hot or very cold weather due to the risk of hyper-, hypothermia. Prochlorperazine should be used cautiously in the elderly owing to their susceptibility to drugs acting centrally on the nervous system. 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 prochlorperazine, e.g. orthostatic hypotension, with effects due to the underlying disorder.

• It should be used with caution in patients with cardiovascular disease or family history of QT prolongation. As with other neuroleptics, cases of QT interval prolongation have been reported with prochlorperazine very rarely (see section 4.8). The risk-benefit should be fully assessed before prochlorperazine treatment is commenced, and patients with predisposing factors for ventricular arrhythmias, (e.g. cardiac disease; metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesaemia; starvation; alcohol abuse; concomitant therapy with other drugs known to prolong the QT interval) should be carefully monitored (biochemical status and ECG), particularly during the initial phase of treatment.

• Acute withdrawal symptoms, including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.
- 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 prochlorperazine and preventative measures undertaken.

- 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. Prochlorperazine should be used with caution in patients with stroke risk factors.

**Increased Mortality in Elderly people with Dementia**
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small 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. Prochlorperazine is not licensed for the treatment of dementia-related behavioural disturbances.

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

**Adrenaline (epinephrine):** Adrenaline (epinephrine) must not be used in patients who have overdosed with prochlorperazine maleate. (See section 4.9).

**Anticholinergic agents:** Anticholinergic agents may reduce the antipsychotic effects of neuroleptics and mild anticholinergic effect of neuroleptics may be enhanced by other anticholinergic agents, possibly leading to constipation, heat stroke, etc.

**Antiepileptics:** Due to liver enzyme induction concomitant use of antiepileptics, including barbiturates may lower the seizure threshold.

**Antihypertensive:** The hypotensive effect of most antihypertensive agents, especially alpha-adrenoceptor blocking agents and calcium channel blockers, may be exaggerated by neuroleptics.

**Anti-parkinson agents:** Where treatment for neuroleptics-induced extrapyramidal symptoms is required, anticholinergic anti-parkinson agents should be used in preference to levodopa, since neuroleptics antagonise the anti-parkinsonian action of dopaminergics.

Cimetidine: Plasma concentrations of prochlorperazine may be affected by cimetidine. Reports have shown plasma levels of prochlorperazine to increase and decrease. Excessive sedation may occur and a dosage reduction of
prochlorperazine may be required. Monitoring should be considered if taken concurrently.

**CNS depressants:** The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol, general anaesthetics, barbiturates, opioid analgesics, anxiolytics and hypnotics. Respiratory depression may occur.

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

**Drugs which prolong the QT interval:** There is an increased risk of ventricular arrhythmias when neuroleptics are used concurrently with drugs which prolong the QT interval, including certain antiarrhythmics, sotalol, antidepressants (tricyclics), antihistamines (terfenadine) and other antipsychotics (see section 4.8).

**Lithium:** In patients treated concurrently with neuroleptics and lithium, there is an increased risk of extrapyramidal effects and the possibility of neurotoxicity.

**Ritonavir:** Increases or decreases in the plasma concentration of a number of drugs including ritonavir have been reported.

**Sibutramine:** Increased risk of CNS toxicity in concomitant use with sibutramine

**Sulfonylureas:** The hypoglycaemic effect of sulfonylureas may possibly be antagonised by prochlorperazine. The dose of the hypoglycaemic agent may need to be increased.

Caution in concomitant use with drugs that cause electrolyte imbalance.

Some drugs interfere with the absorption of neuroleptics, these include antacids, kaolin, lithium, anti-parkinson drugs.

The action of some drugs may be opposed by neuroleptics these include amfetamine, pramipexole, ropinirole, apomorphine, levodopa, lisuride, bromocriptine, cabergoline, pergolide, clonidine, guanethidine, adrenaline (ephinephrine).

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

There is inadequate evidence of the safety of prochlorperazine in human pregnancy. There is evidence of harmful effects in animals. 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 3-4cm. Possible adverse effects on the neonate include lethargy or paradoxical hyperexcitability, tremor and a low Apgar score. Neonates exposed to antipsychotics (including prochlorperazine) 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.

Breast-feeding
Phenothiazines may be excreted in breast milk, breast-feeding should be suspended during treatment.

4.7. Effects on Ability to Drive and Use Machines

Transient drowsiness may occur in some patients during the initial stages of therapy and patients should be advised against the performance of potentially hazardous tasks such as driving a car or operating machinery until the effect has been ascertained.

4.8 Undesirable effects

Blood and the lymphatic system disorders: Mild leucopenia occurs in up to 30% of patients on prolonged high dosage. Agranulocytosis may occur rarely; it is not dose related. The occurrence of unexplained infections or fever requires immediate haematological investigation. (See section 4.4). Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs-Frequency unknown.

Endocrine disorders: Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea and impotence. Nervous system disorders: Agitation and insomnia are minor side-effects. Parkinsonism (Parkinsonism is commoner in adults and the elderly) 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. It is common just for tremor to occur. If tardive dyskinesia occurs it is usually, but not necessarily, after prolonged or high dosage. It can even occur after treatment has been stopped. Therefore, dosage should be kept low whenever possible. Acute dyskinesias and dystonia, usually transitory, are commoner in children and young adults, and usually occur within 4 days of treatment or after dose increases. Akathisia characteristically occurs after large initial doses. Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) may occur with any neuroleptic.
Eye disorders: Ocular changes have been noted in some individuals who have received chlorpromazine continuously for long periods (4-8 years). This could possibly happen with prochlorperazine.

Cardiac disorders: These include cardiac arrhythmias including atrial arrhythmia, A-V block, ventricular fibrillation and ventricular tachycardia (rare). QT prolongation, sudden death, cardiac arrest and torsades de points. Pre-existing cardiac disease, or a family history of QT prolongation, old age, hypokalaemia and concurrent use of other drugs known to prolong the QT interval may predispose patients to these effects. Other effects include ECG changes, usually benign, include ST depression, U-waves and T-wave changes. (Some of these effects are class specific to neuroleptics).

Vascular disorders: Hypotension, usually postural, commonly occurs. Elderly or volume depleted patient are particularly susceptible.

Respiratory, thoracic and mediastinal disorders: Respiratory depression is possible in susceptible patients. Nasal stuffiness is a minor side-effect.

Gastrointestinal disorders: Dry mouth is a minor side effect.

Hepato-biliary disorders: Jaundice, usually transient, 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 obstructions 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.

Pregnancy, puerperium and perinatal conditions:

Frequency not known: Drug withdrawal syndrome neonatal (see section 4.6).

Skin and subcutaneous tissue disorders: Contact skin sensitisation is a serious but rare complication in those frequently handling preparations of certain phenothiazines; the greatest care must be taken to avoid contact of the drug with the skin. The development of a metallic greyish-mauve colouration of the exposed skin has been noted in some individuals, mainly females, who have received chlorpromazine continuously for long periods (4-8 years). This could possibly happen with prochlorperazine. Patients on high dosage should be warned that they may develop photosensitivity in sunny weather and should avoid exposure to direct sunlight. Skin rashes of all kinds are also seen.

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; website: www.mhra.gov.uk/yellowcard

4.9. Overdose

Symptoms of phenothiazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, ECG changes, ventricular arrhythmias and hypothermia. Severe extrapyramidal dyskinesias may occur.
If the patients 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. Adrenaline (Epinephrine) must not be used in patients who have overdosed with prochlorperazine maleate. Generalised vasodilatation may result in circulatory collapse; raising the patient's legs may suffice, in severe cases, volume expansion by iv 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 (epinephrine). Ventricular or supraventricular tachy-arrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life threatening, appropriate anti-arrhythmic therapy may be considered. Avoid lidocaine and, as far as possible, long acting anti-arrhythmic drugs. Pronounced CNS depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine (5-10mg) or orphenadrine (20-40mg) administered intramuscularly or intravenously. Convulsions should be treated with iv diazepam. Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium may be tried.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Phenothiazines with piperazine structure
Prochlorperazine maleate is a phenothiazine.
ATC code: NO5A B04

Prochlorperazine has a wide range of activity arising from its depressant actions on the CNS and its alpha-adrenergic blocking and weaker anti-muscarinic properties. It inhibits dopamine and prolactin-release-inhibitory factor, thus stimulating the release of prolactin. The turnover of dopamine in the brain is increased. There is evidence that the antagonism of central dopaminergic function is related to the therapeutic effect in psychotic conditions.
Prochlorperazine has sedative properties but tolerance to the sedation usually develops rapidly. Prochlorperazine has anti-emetic, anti-pruritic, serotonin-blocking, and weak antihistamine properties and slight ganglion-blocking activity. It inhibits the heat regulating centre, can relax smooth muscle and has membrane stabilising and hence local anaesthetic properties. Its actions on
the autonomic system produce vasodilatation, hypotension and tachycardia. Salivary and gastric secretions are reduced.

5.2 Pharmacokinetic properties

Prochlorperazine is well absorbed from the GI tract but is subject to considerable first pass metabolism from the gut wall. It is also extensively metabolised in the liver and is excreted in the urine and bile. Plasma concentrations following oral administration are much lower than those following intramuscular injection, and are subject to wide inter-subject variation. There is no simple correlation between plasma concentrations of prochlorperazine and its metabolites, and therapeutic effect. Prochlorperazine may be metabolised by hydroxylation and conjugation with glucuronic acid, N-oxidation, oxidation of the sulfur atom and dealkylation. Plasma half-life is reported to be only a few hours but elimination of the metabolites may be very prolonged. Prochlorperazine is extensively bound to plasma proteins, widely distributed in the body (it crosses the blood/brain barrier) and its metabolites cross the placental barrier and are excreted in milk. The rate of metabolism and excretion decreases in old age.

5.3. Preclinical Safety Data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Also contains:
Lactose monohydrate
Magnesium stearate
Maize starch
Microcrystalline cellulose (E460).

6.2. Incompatibilities

None known.

6.3 Shelf life

Shelf-life
Three years from the date of manufacture (PVC blister packs).

Two years from the date of manufacture (polypropylene containers; polyethylene containers; amber glass bottles).

6.4. **Special Precautions for Storage**

Store below 25°C in a dry place. Protect from light.

6.5 **Nature and contents of container**

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene tablet containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass bottles with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs and cartons:

a) Carton: Printed carton manufactured from white folding box board.
b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-6g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 28, 30, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250s, 500s, 1000s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material.

Maximum size of bulk packs: 50,000.

6.6. **Instruction for Use/Handling**

Not applicable.

7 **MARKETING AUTHORISATION HOLDER**

Actavis UK Limited
(Trading style: Actavis)
Whiddon Valley
BARNSTAPLE
N Devon
EX32 8NS
8. MARKETING AUTHORISATION NUMBER(S)

PL 00142/0312

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th May 1992
Date of latest renewal: 6th May 1997

10. DATE OF REVISION OF THE TEXT

03/02/2017