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

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 (particularly 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

Adults

Indication	Dosage
Prevention of nausea and vomiting	5 – 10 mg b.d. or t.d.s.
Treatment of nausea and vomiting	20 mg stat, followed if necessary by 10 mg two hours later.
Vertigo and Meniere's syndrome	5 mg t.d.s. 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	15 – 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	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 12.5 mg at 4 – 7 days interval until a satisfactory response is obtained. After some weeks at the effective dosage, an attempt should be made reduce this dosage. Total daily amounts as small as 50 mg or even 25 mg have sometimes been found to be effective.

Paediatric population

Indication	Dosage
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 a day. Prochlorperazine is not recommended for children weighing less than 10 kg or below 1 year of age.

Elderly

A lower dose is recommended (see section 4.4).

Method of Administration
For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance, to other phenothiazines or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Prochlorperazine should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis, prostate hypertrophy, or a history of narrow angle glaucoma or agranulocytosis.

Monitoring advice

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.

Blood disorders

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

Neuroleptic malignant syndrome

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.

Withdrawal

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.

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

QT prolongation

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 Prochlorperazine 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 with Prochlorperazine and during the initial phase of treatment, or as deemed necessary during the treatment (see also sections 4.5 and 4.8).

Psychiatric disorders

As with all antipsychotic drugs, Prochlorperazine 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.

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.

Photosensitivity

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

Skin reactions

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).

Elderly

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.

Prochlorperazine should be used cautiously in the elderly owing to their susceptibility to drugs acting on the central nervous system and a lower initial dosage is recommended. 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 the effects due to the underlying disorder.

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 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.

Prochlorperazine tablets are not licensed for the treatment of dementia-related behavioural disturbances.

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.

Paediatric population

Prochlorperazine has been associated with dystonic reactions particularly after a cumulative dosage of 0.5 mg/kg. It should therefore be used cautiously in children.

Venous thromboembolism

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.

Hyperglycaemia

Hyperglycaemia or intolerance to glucose has been reported in patients treated with antipsychotic phenothiazines. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on Prochlorperazine tablets, should get appropriate glycaemic monitoring during treatment (see section 4.8).

Hypersensitivity

Hypersensitivity reactions including anaphylaxis, urticaria and angioedema have been reported with Prochlorperazine use. In case of allergic reactions, treatment with Prochlorperazine must be discontinued and appropriate symptomatic treatment initiated (see section 4.8).

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Adrenaline must not be used in patients overdosed with prochlorperazine maleate. (See section 4.9).

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

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

Some drugs interfere with absorption of neuroleptic agents: antacids, anti-Parkinson drugs and lithium.

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.

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

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

The action of some drugs may be opposed by phenothiazine neuroleptics; these include amfetamine, levodopa, clonidine, guanethidine, adrenaline.

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.

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

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.

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.

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

Some phenothiazines are potent inhibitors of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. 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

Pregnancy

Animal studies are insufficient with respect to reproductive toxicity. However, potential harmful effect in animals cannot be ruled out. There is inadequate evidence of safety in pregnancy. Data from epidemiological studies do not suggest a risk of congenital malformations in children exposed in utero to Prochlorperazine.

As a precautionary measure, Prochlorperazine should be avoided during pregnancy unless the potential benefits outweigh the potential risks.

Neuroleptics may occasionally prolong labour and at such time should be withheld until the cervix is dilated 3 – 4 cm. Possible adverse effects on the neonate include lethargy or paradoxical hyperexcitability, tremor and 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 milk, therefore breast-feeding should be suspended during treatment.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients should be warned about drowsiness during the early days of treatment and advised not to drive or operate machinery.

4.8 Undesirable effects

Generally, adverse reactions occur at a low frequency; the most common reported adverse reactions are nervous system disorders.

Blood and lymphatic system disorders:

• A mild leukopenia occurs in up to 30% of patients on prolonged high dosage.

• Agranulocytosis may occur rarely: it is not dose related (see section 4.4).

Immune system disorders:

• Anaphylactic reactions.

• Type I hypersensitivity reactions such as angioedema and urticaria.

Endocrine disorders:

• Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea and impotence.

Metabolism and nutrition disorders:

• Hyponatraemia.

• Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Nervous system disorders:

• Acute dystonia or dyskinesias, including oculogyric crisis, usually transitory are commoner in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases.

• Akathisia characteristically occurs after large initial doses.

• 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.

• 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.

• Insomnia and agitation may occur.

• Convulsions.

Eye disorders:

Ocular changes and the development of metallic greyish-mauve coloration of exposed skin have been noted in some individuals, mainly females who have received chlorpromazine continuously for long periods (four to eight years). This could possibly happen with Prochlorperazine.

Cardiac disorders:

• 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 causes of cardiac origin (see section 4.4), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Vascular disorders:

• Hypotension, usually postural, commonly occurs. Elderly or volume depleted subjects are particularly susceptible; it is more likely to occur after intramuscular injection.

• Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs – frequency not known.

Respiratory, thoracic and mediastinal disorders:

• Respiratory depression is possible in susceptible patients.

• Nasal stuffiness may occur.

Gastrointestinal disorders:

Dry mouth may occur.

Hepatobiliary disorders:

Jaundice, usually transient, occurs in a very small percentage of patients taking neuroleptics. A premonitory sign may be 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 (see section 4.4).

Skin and subcutaneous tissue disorders:

• Contact skin sensitisation may occur rarely in those frequently handling preparations of certain phenothiazines (see section 4.4).

• 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.

Pregnancy, puerperium and perinatal conditions:

Drug withdrawal syndrome neonatal (see section 4.6) – frequency not known.

General disorders and administration site conditions:

Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) may occur with any neuroleptic (see section 4.4).

Intolerance to glucose, hyperglycaemia (see section 4.4)

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

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: Psycholeptics, antipsychotics, phenothiazines with piperazine structure.
ATC code: N05AB04.

Prochlorperazine maleate is a potent phenothiazine neuroleptic.

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

There are no preclinical 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

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

6.2. Incompatibilities

None known.

6.3 Shelf-life

Three years from the date of manufacture (PVC blister packs)

Two years from the date of manufacture (polypropylene containers).

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 tablet containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids.
Pack size: 1000s

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/0312

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

12/05/2023