SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prochlorperazine Maleate Tablets BP 25mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prochlorperazine Maleate 25 mg, also contains lactose and sucrose
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vertigo due to Meniere's syndrome, labyrinthine and other causes, nausea and vomiting from whatever cause including that associated with migraine, schizophrenia and other psychotic disorders, short-term management of anxiety.

4.2 Posology and method of administration

To be taken orally.

Adults:

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 30 mg daily. 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 initiaily 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 75-100 mg. Amounts as small as 50 mg or 25 mg have been found to be effective. Initially 12.5 mg twice daily for seven days, the daily amount being subsequently increased by 12.5 mg at four to seven day intervals until a satisfactory response is obtained. An attempt should be made to reduce this dosage after some weeks at the effective dosage.

Children:

Prevention and treatment nausea and vomiting: The dosage is 25 micrograms/kg bodyweight
two or three times a day.

It is recommended that the 5 mg tablet should be used.
Not recommended for children weighing less than 10 kgs.

Elderly:

Prochlorperazine Maleate should be used cautiously in this group of psychotic disorders.

Lower initial dosage is recommended. Care should also be taken not to confuse adverse effects of Prochiorperazine Maleate, e.g. orthostatic hypotension, with effects due to the primary disorder.

4.3 Contraindications

Prochlorperazine belongs to Phenothiazines (antipsychotic drugs). Antipsychotic drugs may be contraindicated in comatose states, CNS depression and phaeochromocytoma. Most antipsychotics are best avoided during pregnancy, unless essential and is advisable to discontinue breast-feeding during treatment.

4.4 Special warnings and precautions for use

Prochlorperazine should be used with caution in patients with renal or liver dysfunction, cardiovascular disease, epilepsy, Parkinson's disease, depression, hypothyroidism, myasthenia gravis and prostrate hypertrophy.

Prochlorperazine should be avoided in patients known to be hypersensitive to phenothiazines or with a history of narrow angle glaucoma.

Caution is also required in patients with severe respiratory disease, blood

dyscrasias, a history of jaundice or agranulocytosis.

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.

Acute withdrawal symptoms, including nausea, vomiting and insomnia have very rarely been reported following 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.

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; alcoholic 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.

It should be used with caution in the elderly who are particularly susceptible to postural hypotension and to risk of hyper-/hypothermia during very hot or very cold weather. Lower initial dose is recommended in the elderly. There is an increased risk of drug-induced Parkinsonism in the elderly particularly after prolonged use.

Photosensitisation may occur with higher dosages, patients should avoid direct sunlight.

Patients with rare hereditary problems of galactose / fructose intolerance, Lapp lactase deficiency or glucose/galactose malabsorbtion or sucrase- isomaltase insufficiency should not take Prochlorperazine.

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

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 preventive measures undertaken.

4.5 Interaction with other medicinal products and other forms of interaction

There is an increased risk of ventricular arrhythmias when prochlorperazine is used concurrently with certain anti-arrhythmics (e.g., amiodarone, disopyramide, procainamide, quinidine) where the QT interval is prolonged, tricyclic antidepressants, other antipsychotics, (e.g., pimozide), moxifloxacin and sotalol.

The depressant actions of the drug may be intensified 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. An enhanced hypotensive effect is also seen when antipsychotics are given with general anaesthetics.
Anticholinergic agents may reduce the antipsychotic effect of neuroleptics. The mild anticholinergic effect of neuroleptics may be enhanced by tricyclic antidepressants or other anticholinergic drugs and this may lead to heat stroke, constipation, etc.
Phenothiazines antagonise the anticonvulsant effect of barbiturates and certain anti-epileptics (e.g., carbamazepine, ethosuximide, oxcarbazepine, primidone, phenytoin, valproate).

The action of certain drugs may be opposed and these include amphetamine, levodopa, clonidine, guanethidine and adrenaline.

Drugs interfering with absorption include antacids, anti-Parkinson drugs and lithium. Neurotoxicity has been reported with 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.
There is an increased risk of agranulocytosis when neuroleptics are used concurrently with drugs of a myelosuppressive potential such as carbamazepine, certain antibiotics and cytotoxics.
Increases or decreases in the plasma concentration of a number of drugs, e.g. propranolol, phenobarbitone and ritonavir have been reported but are of no 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.

High doses of Prochlorperazine reduce the response to hypoglycaemic agents and accordingly the dosage of these may have to be raised.

4.6 Fertility, pregnancy and lactation

Prochlorperazine is contraindicated in pregnancy unless the physician considers it essential.

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, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully.

Other possible adverse effects on the neonate include lethargy or paradoxical hyperexcitability, tremor and low Apgar score.

It may occasionally prolong labour and at such a time should be withheld until the cervix is dilated 3-4 cm. It may be excreted in breast milk, breast-feeding should be suspended during treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Cardio-respiratory:

Hypotension, usually postural, occurs commonly. The elderly are particularly susceptible. Hypotension and interference with temperature regulation are dose-related side effects and are liable to cause dangerous falls and hypo/hyperthermia in the elderly.

Cardiac arrhythmias, including auricular arrhythmia A-V block, ventricular tachycardia and fibrillation have been reported. This may be related to dosage. Pre-existing cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose cardiac arrhythmias. ECG changes include widened QT interval, ST depression, U-waves and T-wave changes.

Respiratory depression is possible in susceptible patients.

Blood dyscrasias:

Mild leukopaenia occurs in up to 30% of patients on prolonged high dose therapy. Agranulocytosis may occur rarely. Any occurrence of unexplained infections or fever requires haematological investigation.

Extrapyramidal:

Acute dystonias or dyskinesias, usually transitory are more common in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases.

Akathisia 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. Symptoms remit if the drug is withdrawn and may be suppressed with anticholinergic drugs.

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 and in the elderly, the treatment must be frequently reviewed.

Skin and eyes:

Contact skin sensitisation is a serious but rare complication, the greatest care must be taken to avoid contact of the drug with the skin. Skin rashes, corneal and lens opacities and purplish pigmentation of the skin, cornea, conjunctiva and retina 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. 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 (4-8 years) and that this could possibly happen with Prochlorperazine.

Jaundice, usually transient, occurs in a very small percentage of patients. 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; the frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Treatment should be withheld on the development of jaundice.

Minor side effects of neuorleptics are agitation, anticholinergic symptoms (such as, blurred vision, constipation, difficulty with micturition, dry mouth), apathy, convulsions, excitement, GI disturbances, nasal stuffiness, headache, confusion and insomnia.

Endocrine:

Hyperprolactinaemia, which may result in menstrual disturbances, galactorrhoea, gynaecomastia, amenorrhoea, impotence and weight gain.

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

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

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs- Frequency unknown.

4.9 Overdose

Symptoms of overdose include drowsiness or loss of consciousness, hypotension, tachycardia, E.C.G. changes, ventricular arrhythmias and hypothermia. Severe extra-pyramidal dyskinesias may occur.

If the patient is seen up to 6 hours after ingestion of a toxic dose, gastric lavage may be attempted. Activated charcoal should be given. There is no specific antidote. Treatment is supportive.

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. Avoid the use of adrenaline.

Ventricular or supraventricular tachy-arrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. Appropriate anti-arrhythmic 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 (5-10 mg) or orphenadrine (20-40 mg 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

Prochlorperazine has a wide range of activity arising from its depressant actions on the Central Nervous System and its alpha-adrenergic blocking and weaker anticholinergic activities. It is a dopamine inhibitor; it inhibits prolactin-release-inhibitory factory, considered to be dopamine, thus stimulating the release of prolactin. The turnover of dopamine in the brain is also increased.

It has anti-emetic, antipruritic, serotonin-blocking and weak antihistamine properties and slight ganglion-blocking activity. It inhibits the heat regulating centre so that the patient tends to acquire the temperature of his surroundings. It is analgesic and can relax skeletal muscle. Its actions on the autonomic system produce vasodilation, hypotension and tachycardia. Salivary and gastric secretions are reduced.

5.2 Pharmacokinetic properties

Prochlorperazine is readily absorbed from the gastro-intestinal tract but is subject to considerable first-pass metabolism in the gut wall. It is also extensively metabolised in the liver and is excreted in the urine and faeces in the form of numerous active and inactive metabolites; there is evidence of enterohepatic recycling.

Although the plasma half-life has been reported to be only a few hours, it has a very prolonged terminal elimination phase of up to about 3 weeks. Its duration of therapeutic effect can range from a few days to several weeks or possibly longer.

It is very extensively bound to plasma proteins. It is widely distributed in the body and crossed the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Its metabolites also cross the placental barrier and are excreted in breast milk.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Pre-gelatinised maize starch
Sucrose
Sodium starch glycollate
Magnesium stearate
Purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

Polystyrene/polypropylene containers: 36 months
PVC/Aluminium blister-packs: 24 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

High density polystyrene with a polythene lid and/or polypropylene containers with polypropylene or polythene lid, and polyurethane/polythene inserts. Packs of 100 and 500.

PVC/Aluminium blister-packs. Packs of 28 and 84.

6.6. Special precautions for disposal <and other handling>

No special precautions

7 MARKETING AUTHORISATION HOLDER

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