SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prochlorperazine Tablets 5mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prochlorperazine Maleate 5.00mg, also contains lactose
For excipients see 6.1

3 PHARMACEUTICAL FORM

Tablet
Almost white or pale buff coloured 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

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 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 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 of 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 kg or below 1 year of age.

Elderly:

Prochlorperazine 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 Prochlorperazine, e.g. orthostatic hypotension, with effects due to the primary disorder.

Method of administration
Oral

4.3 Contraindications

Prochlorperazine belongs to Phenothiazines (antipsychotic drug). Antipsychotic drugs may be contraindicated in comatose states.
Known hypersensitivity to prochlorperazine or to any of the other ingredients listed in section 6.1.

4.4 Special warnings and precautions for use

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

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

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

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.

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.

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.

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).

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

Depression:
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.

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 who are particularly susceptible to postural hypotension and to risk of hyper/hypothermia during very hot or very cold weather. Lower initial dosage is recommended in the elderly. 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 is not licensed for the treatment of dementia-related behavioural disturbances.

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 preventive measures undertaken.

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

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 should get appropriate glycaemic monitoring during treatment (see section 4.8).

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

4.5 Interaction with other medicinal products and other forms of interaction

Adrenaline must not be used in patients overdosed with Prochlorperazine (see section 4.9).

There is an increased risk of ventricular arrhythmias when prochlorperazine is used concurrently with certain antiarrhythmics (e.g. amiodarone) where the QT interval is prolonged, tricyclic antidepressants, other antipsychotics, (e.g. pimozide and thioridazine), moxifloxacin and sotalol and drugs causing electrolyte imbalance.

The CNS 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. The mild anticholinergic effect 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, 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 and lithium. Neurotoxicity has been reported with lithium.

Where treatment for neuroleptic-induced extrapyramidal symptoms is required, anticholinergic anti-parkinsonian agents should be used in preference to levodopa, since neuroleptics antagonise the anti-parkinsonian 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.

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.

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, it should be avoided in pregnancy unless the potential benefits outweigh the potential risks.

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 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

It may be excreted in breast milk, therefore 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

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

Immune system disorders:
- Type I hypersensitivity reactions such as angioedema and urticaria.

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).

Endocrine disorders:
- Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea and impotence

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 unknown

Gastrointestinal disorders:
Dry mouth may occur.

Metabolism and nutrition disorders:
- Hyponatraemia
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

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

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)

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose include drowsiness or loss of consciousness, hypotension, tachycardia, E.C.G. changes, ventricular arrhythmias and hypothermia. Severe extrapyramidal 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.

Generalised vasodilatation may result in circulatory collapse; raising the patient's legs may suffice. 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. If persistent or life threatening, 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

Pharmacotherapeutic group: Antipsychotics, ATC code: N05AB04

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 patients tend 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

No relevant information additional to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package or container.

6.5 Nature and contents of container

High density polystyrene with polythene lid and/or polypropylene containers with polypropylene or polythene lid, and polyurethane/polythene inserts. Packs of 28, 30, 56, 60, 84, 90, 100, 500 and 1000.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special precautions.

7 MARKETING AUTHORISATION HOLDER

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PL 42976/0009

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03/09/2020