SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Chlorpromazine Tablets BP 25 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlorpromazine Hydrochloride BP 25 mg

3 PHARMACEUTICAL FORM

Sugar Coated Tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Chlorpromazine is a phenothiazine neuroleptic and is indicated in the following conditions.

1. Psychotic conditions (especially paranoid) including schizophrenia, mania and hypomania.

2. As an adjunct in the short term management of anxiety psychomotor agitation excitement, violent or dangerously impulsive behaviour.

3. Nausea or vomiting associated with terminal illness, where other agents are ineffective or unavailable.

4. Induction of hypothermia to prevent shivering and cause vasolidation.

5. Intractable hiccup.

6. Childhood schizophrenia and autism.

4.2 Posology and method of administration

Method of Administration:

Tablets are to be taken orally with a drink of water.

Posology:

Dosage:
Dosage varies both with the individual and with the purpose for which the drug is being used. The dosage should be low to begin with and increased, gradually, under close supervision until the optimum level of control is achieved.

Dosage in Schizophrenia, Other Psychoses Anxiety and Agitation etc:

Adults:
Initially 25mg three times daily or 75mg at bedtime, increasing by daily amounts of 25mg to the effective maintenance dose. The usual maintenance dose is in the range of 75 to 300mg daily, although some patients may require up to 1.0g daily.

Children:

(i) Aged under 1 year:
Chlorpromazine should generally not be used unless the need is life-saving.

(ii) Age 1 to 5 years: 0.5mg/kg every 4 to 6 hours to a maximum daily dosage of 40mg.

(ii) Age 6 to 12 years: One-third to half the adult dose to a maximum daily dosage of 75mg.

Elderly or Debilitated Patients:

Initially one-third to half the usual adult dose with a more gradual increase in dosage.

Dosage in Hiccup:

Adults:	25-50mg three to four times daily
Children:	No information available.
Elderly:	One-third to half adult dose initially, with a more gradual increase in dosage.

Dosage in Nausea and Vomiting of Terminal Illness:

Adults: ½ to 1 tablet every 4 to 6 hours
Children:
(i) Age under 1 year: Chlorpromazine should generally not be used unless the need is life-saving.

(ii) Age 1 to 5 years: 0.5mg/kg every 4 to 6 hours. The maximum daily dosage should not exceed 40mg.

(iii) Age 6 to 12 years: 0.5mg/kg every 4 to 6 hours. The maximum daily dosage should not exceed 75mg.

Elderly or Debilitated Patients:
Initially one-third to half the adult dose. The subsequent dosage should be adjusted under close supervision to obtain control.

4.3 Contraindications

Chlorpromazine is contraindicated in patients with a known hypersensitivity to the drug. Chlorpromazine is also contraindicated in comatose patients, including those under the influence of alcohol or other central nervous system depressants.

4.4 Special warnings and precautions for use

Chlorpromazine should be avoided whenever possible in patients with hepatic or renal dysfunction, cardiac failure, phaeochromocytoma, hypothyroidism, bone marrow depression, epilepsy, parkinsons' disease, myasthenia gravis, prostatic hypertrophy or a history of narrow angle glaucoma.

Chlorpromazine should be used with caution in the elderly, especially during very hot or very cold weather because of the risk of hyper or hypothermia.

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 Chlorpromazine Tablets and preventive measures undertaken.

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 cause of the increased risk is not shown.

Chlorpromazine Tablets are not licensed for the treatment of dementia-related behavioural disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol, barbiturates and other sedatives may intensify. The CNS depressant effects of Chlorpromazine and respiratory depression may occur.

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

Chlorpromazine has mild anticholinergic activity which may be enhanced by other anticholinergic drugs.

Anticholinergic drugs may decrease the antipsychotic effect of Chlorpromazine.

Chlorpromazine may oppose the action of some drugs, including Amphetamine, levodopa, Adrenaline, Clonidine and Quanethidine.

Some drugs interfere with the absorption of neuroleptic agents e.g. antacids, lithium, anti-Parkinsonian agents. Although increases or decreases have been observed in some plasma concentrations of a number of drugs including Propranolol and Phenobarbitone. These were not of clinical significance. At high dosage, Chlorpromazine reduces the response to hypoglycaemic agents, which may require an increase in dosage of the latter.

Clinically significant adverse drug interactions with alcohol, Guanethidine and hypoglycaemic agents have been reported. Adrenaline must not be used in cases of overdosage with Chlorpromazine. Other interactions are of theoretical interest and are not of a serious nature.

Concomitant administration of Desferrioxamine and Prochlorperazine has been reported to cause a transient metabolic encephalopathy with loss of consciousness for 48 to 72 hours. The possibility of a similar occurrence with Chlorpromazine exists, because it shares many of the pharmacological activities of Prochlorperazine.

4.6 Fertility, Pregnancy and lactation

The safety of Chlorpromazine in pregnancy has not been established, although the drug has been in wide use for many years without apparent ill consequence. There is evidence of harmful effects in animals. As with other drugs Chlorpromazine should be avoided during pregnancy unless it is considered essential by the physician, labour may occasionally be prolonged

by Chlorpromazine and therapy should be delayed until the cervix is dilated 3 to 4 cms.
Neonates exposed to antipsychotics (including chlorpromazine) 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.
Other possible effects on the neonate include lethargy, paradoxical hyperexcitability and a low APGAR score.
Chlorpromazine is excreted in breast milk and breast feeding should be suspended during treatment.

4.7 Effects on ability to drive and use machines

Chlorpromazine may cause drowsiness, especially during the early days of therapy and patients should be warned not to drive or operate machinery if affected.

4.8 Undesirable effects

Minor side effects include nasal stuffiness, dry mouth, insomnia and agitation.

Cardiovascular hypotension, especially postural, is relatively common and elderly patients or subjects with volume depletion are particularly susceptible. Cardiac arrhythmias have been reported in patients receiving neuroleptic agents and may be dose-related. They include atrial arrhythmia, A-V block, ventricular tachycardia and fibrillation. Pre-existing cardiac disease, hypokalaemia, concurrent use of tricyclic antidepressants and old age may predispose to development of arrhythmia. ECG changes may occur, including widened QT interval, ST depression, U waves and T wave changes.

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

Blood: Mild leucopenia may occur in up to 30% of patients on prolonged high dosage. Agranulocytosis may occur rarely and is not dose-related. Unexplained infections or pyrexia require immediate haematological investigations.

Respiratory: Clinical doses of the neuroleptics usually have little effect on respiration. However, respiratory depression may occur in susceptible patients.

Hepatic: A very small percentage of patients may develop jaundice, which is usually transient and which may be preceded by sudden pyrexia after one to three weeks of treatment. The jaundice is obstructive in type and is frequently accompanied by an eosinophilia, indicating the allergic nature of the event. Chlorpromazine therapy should be withdrawn if jaundice occurs.

Extrapyramidal: Acute dystonic or dyskinetic reactions may occur. These are usually transitory, are more common in children and young adults and are more likely to occur within the first four days of treatment or after dosage increases. Akathisia may occur, characteristically following large initial doses.

Neutoleptic-induced parkinsonism is more common in adults and the elderly and usually takes weeks or months of treatment to develop. Tremor is a common sign but rigidity, akinesia or other features of parkinsonism may also occur.

If tardive dyskinesia occurs, it is usually, although not always, associated with prolonged or high dosage. It may occur after treatment has been discontinued. To reduce the likelihood of tardive dyskinesia, the dosage should be kept low whenever possible.

Skin & Eyes: Various skin rashes may occur during therapy with Chlorpromazine. Photosensitivity eruptions may occur and patients receiving high dosage should be advised to avoid exposure to direct sunlight. Contact skin sensitisation is a rare but serious complication in persons who frequently handle Chlorpromazine preparations and particular care should be taken to avoid contact of the drug with the skin.

Ocular changes and a metallic greyish-mauve discoloration of exposed skin has been reported in some patients, mainly females, who received Chlorpromazine continuously for long periods of between four and eight years.

Endocrine: Hyperprolactinaemia has been reported and may result in galactorrhoea, gynaecomastia or amenorrhoea, impotence has been reported.

Neuroleptic Malignant Syndrome: The syndrome may occur with use of any neuroleptic agent. Symptoms include clouding of consciousness, rigidity and other extrapyramidal effects, and autonomic dysfunction, most importantly hyperpyrexia. Treatment involves the immediate cessation of neuroleptic therapy and symptomatic management as appropriate.

Pregnancy, puerperium and perinatal conditions: Drug withdrawal syndrome neonatal (see 4.6) . The frequency of this adverse drug reaction is not known.

4.9 Overdose

Symptoms of overdosage may include drowsiness or loss of consciousness, hypotension, tachycardia, ventricular, arrhythmias, acute extrapyramidal reactions and hypothermia. There is no specific antidote and treatment is essentially symptomatic and supportive. The stomach should be emptied by aspiration and lavage and activated charcoal should be given. Circulatory collapse may respond to elevation of the lower limbs, although volume expansion with intravenous fluids may be required. Use of a positive inotropic agent such as dopamine may be considered if circulatory collapse does not respond to volume expansion; peripheral vasoconstrictor agents are not generally recommended and adrenaline should be avoided.

Tachyarrythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. Anti-arrhythmic therapy may be considered for persistent or life-threatening arrhythmias; lignocaine should be avoided and, as far as possible, so should long-acting anti-arrhythmic drugs.

If severe dystonic reactions occur they usually respond to procylidine 5 to 10mg or orphenadrine 20 to 40mg given intramuscularly or intravenously. Intravenous diazepam may be used to treat convulsions.

Dantrolene sodium together with cooling and general supportive measure may be used to treat the neuroleptic malignant syndrome.

An open airway should be maintained and artificial respiration may be required in severe cases of central nervous system depression.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Chlorpromazine is a dimethylamine derivative of phenothiazine. Although the precise mechanism whereby the therapeutic effects of Chlorpromazine are produced is not known, the principal pharmacological actions are neuroleptic, resulting in the favourable modification of psychotic symptoms. Chlorpromazine also exerts sedative and anti-emetic activity. It has alpha¬-adrenergic blocking and weaker anticholinergic activities.

It is an inhibitory of dopamine and it inhibits prolactin-release-inhibitory factor (considered to be dopamine), thus stimulating the release of prolactin. Chlorpromazine has serotonin-blocking and weak antihistamine properties. It inhibits the heat-regulatine centre so that the subject tends to acquire the ambient temperature.

5.2 Pharmacokinetic properties

Although Chlorpromazine is readily absorbed from the G.I. tract, it undergoes first-pass metabolism in the gut wall and is also extensively metabolised in the liver. Intramuscular administration avoids much of the first-pass metabolism of the drug. Paths of metabolism include hydroxylation and conjugation with glucuronic acid, n-oxidation, oxidation of a sulphur atom and dealkylation. Chlorpromazine is extensively bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Chlorpromazine and its metabolites also cross the placental barrier and are excreted in breast milk.

Although the plasma half-life of Chlorpromazine has been reported to be only a few hours, elimination of metabolites may be very prolonged. Chlorpromazine is excreted in the urine and faeces in the form of numerous active and inactive metabolites.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to a prescriber which is additional to that already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, potato starch, maize starch, sucrose, magnesium stearate, stearic Acid, talc, gelatin, titanium dioxide.

6.2 Incompatibilities

None Known.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in a dry place below 25°C.

6.5 Nature and contents of container

The product is available in packs of 100, 250, 500 and 1000 tablets in securitainers. The container is made up of High Density Polypropylene body and Low Density Polyethylene cap.

6.6 Special precautions for disposal

No special instruction necessary.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/1083

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