SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
   Chlorpromazine 100mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Chlorpromazine Hydrochloride 100.00 mg
   See 6.1 for excipients.

3. PHARMACEUTICAL FORM
   Film-coated tablet
   Round, white, film-coated tablet market ‘CPZ 100’.

4. CLINICAL PARTICULARS
   4.1 Therapeutic indications
   Schizophrenia and other psychoses (especially paranoia), mania and hypomania. In anxiety, psychomotor agitation, excitement, violent or dangerously impulsive behaviour. Is used as an adjunct in the short-term management of these conditions.
   Intractable hiccup.
   Nausea and vomiting in terminal illness (where other drugs have failed or are not available).
   Induction of hypothermia is facilitated by Chlorpromazine Tablets which prevents shivering and causes vasodilatation.
   Childhood schizophrenia and autism.

   4.2 Posology and method of administration
   Dosages should be low to begin with and gradually increased under close supervision until the optimum dosage for the individual is reached. Individuals vary considerably and the optimum dose may be affected by the formulation used.
   Dosage of chlorpromazine in schizophrenia, other psychoses, anxiety and agitation etc.
   Adult:
   Initially 25 mg t.d.s. or 75 mg at bedtime increasing by daily amounts of 25 mg to an effective maintenance dose. This is usually in the range 75 to 300 mg daily but some patients may require up to 1 g daily.
   Children under 1 year:
   Do not use unless need is life saving.
   Children 1-5 years:
   0.5 mg/kg body weight every 4-6 hours to a maximum recommended dose of 40 mg daily.
   Children 6-12 years:
   $\frac{1}{3}$-$\frac{1}{2}$ adult dose to a maximum recommended dose of 75 mg daily.
   Elderly or debilitated patients:
   Start with $\frac{1}{3}$-$\frac{1}{2}$ usual adult dose with a more gradual increase in dosage.
Hiccups

Adult:
25-50 mg t.d.s. or q.d.s.

Children under 1 year:
No information available.

Children 1-5 years:
No information available.

Children 6-12 years:
No information available.

Elderly or debilitated patients:
As for adults.

Nausea and vomiting of terminal illness:

Adults:
10-25 mg every 4-6 hours.

Children under 1 year:
Do not use unless need is life saving.

Children 1-5 years:
0.5 mg/kg every 4-6 hours. Maximum daily dosage should not exceed 40 mg.

Children 6-12 years:
0.5 mg/kg every 4-6 hours. Maximum daily dosage should not exceed 75 mg.

Elderly or debilitated patients:
Initially $\frac{1}{3}-\frac{1}{2}$ adult dose. The physician should then use his clinical judgment to obtain control.

Method of administration: Oral

4.3 Contraindications

Chlorpromazine Tablets should be avoided in patients with liver or renal dysfunction, epilepsy, Parkinson’s disease, hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis, prostate hypertrophy. It should be avoided in patients known to be hypersensitive to phenothiazines or with a history of narrow angle glaucoma. It should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper/hypothermia).

It should be used with caution in patients with risk factor for stroke.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
4.4 Special warnings and precautions for use

Blood Dyscrasias: Agranulocytosis has been reported rarely, most commonly in the first three months of treatment, but occasionally later. Blood counts should be performed if the patient develops signs of a persistent infection. Transient leucopenia can also occur. Other blood dyscrasias including thrombocytopenia and haemolytic anaemia have occurred very rarely.

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.

Chlorpromazine commonly causes increased susceptibility to sunburn and patients should be warned to avoid excessive exposure. Phototoxic or photoallergic reactions may occur. Various skin rashes and reactions, including exfoliative dermatitis and erythema multiforme have been reported. Contact skin sensitivity may be produced by contact with chlorpromazine. The occurrence of antinuclear antibodies has been reported. SLE has very rarely occurred. Chlorpromazine impairs body temperature regulation and cases of severe hypothermia or hyperpyrexia have been reported, usually in association with moderate or high dosage. The elderly or hypothyroid patient may be particularly susceptible to hypothermia. The hazard of hyperthermia may be increased by especially hot or humid weather or by drugs, such as anti-Parkinson agents, which impair sweating. It has also been reported after intramuscular injections of chlorpromazine.

Chlorpromazine can rarely cause obstructive jaundice associated with stasis in biliary canaliculi. It has been thought to be a hypersensitivity reaction and some cases have shown premonitory fever and associated eosinophilia. It has normally been reversible on stopping the drug, but extremely rare cases of progressive liver disease have been reported. In most cases the jaundice has appeared between one to four weeks after the start of the treatment. Chlorpromazine treatment should be withdrawn and not given again.

Transient abnormalities of liver function tests may occur in the absence of jaundice.

Faecal impaction, severe paralytic ileus or megacolon have been reported. The signs of intestinal obstruction may be obscured by the anti-emetic action of chlorpromazine.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Chlorpromazine should be used with caution in patients with risk factors for stroke.

Chlorpromazine should be used with caution in patients with cardiovascular disease or a family history of QT prolongation. Concomitant neuroleptics should also be avoided.

With long-term usage, chlorpromazine can cause increased melanin pigmentation of the skin, which eventually may develop a bluish-grey colouration. Pigment deposits also occur in the eye and other tissues. Permanent deposits, leading to impairment of vision, may develop in the lens. Epithelial keratopathy has been reported. Toxic pigmentary retinopathy, which may cause progressive loss of vision has occurred very rarely, with excessively high doses. Acute withdrawal symptoms including nausea, vomiting and insomnia have rarely been described after abrupt cessation of high doses of chlorpromazine. Gradual withdrawal is advisable.
Anti-Parkinson agents should not be prescribed routinely, because of the possible risks of aggravating anticholinergic side effects of chlorpromazine, of precipitating toxic-confusional states or of impairing its therapeutic efficacy. They should only be given as required.

The elderly are especially susceptible to the sedative and hypotensive effects of Chlorpromazine Tablets.

**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.

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

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

The CNS depressant actions of Chlorpromazine Tablets and other neuroleptic agents may be intensified (additively) by alcohol, cimetidine, opioid, analgesics, barbiturates and other sedatives. Respiratory depression may occur. The hypotensive effect of most antihypertensive drugs especially alpha adrenoceptor blocking agents may be exaggerated by Chlorpromazine Tablets. The mild anticholinergic effect of Chlorpromazine Tablets may be enhanced by other anticholinergic drugs possibly leading to constipation, heat stroke etc. Phenothiazines enhance the hypotensive effect of anaesthetics and calcium channel blockers. Severe postural hypotension may occur with concomitant administration of chlorpromazine and ACE inhibitors.

The action of some drugs may be opposed by Chlorpromazine Tablets; these include amphetamine, levodopa, clonidine, guanethidine, adrenaline.

Anticholinergic agents may reduce the antipsychotic effect of Chlorpromazine Tablets. Some drugs interfere with absorption of neuroleptic agents; antacids, anti-Parkinson, lithium. Increases or decreases in the plasma concentrations of a number of drugs, e.g. propanolol, phenobarbitone have been observed but were not of clinical significance. Phenothiazines increase the risk of ventricular arrhythmias with drugs that prolong the QT interval such as sotalol. The serum concentration of chlorpromazine may be increased by some antimalarial agents.

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

Chlorpromazine should not be taken with QT prolonging drugs, drugs causing electrolyte imbalance and metabolic inhibitors.

Documented clinically significant adverse interactions occur with alcohol, guanethidine and hypoglycaemic agents. Adrenaline must not be used in patients overdosed with Chlorpromazine Tablets. Other interactions are of a theoretical nature and not serious.

### 4.6 Pregnancy and lactation

There is inadequate evidence of the safety of Chlorpromazine Tablets in human pregnancy but it has been widely used for many years without apparent ill consequence. There is evidence of harmful effects in animals. Like other drugs it should be avoided in pregnancy unless the physician considers it essential. It may occasionally prolong labour and at such a time should be withheld until the cervix is dilated 3-4cm. Possible adverse effects on the foetus include...
lethargy or paradoxical hyperexcitability, tremor and low Apgar score. Chlorpromazine Tablets being excreted in milk, breast-feeding should be suspended during treatment.

Neonates exposed to antipsychotics (including Chlorpromazine Tablets 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.

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

Common side effects, particularly with higher dosage and at the start of treatment include drowsiness, sedation, dry mouth, nasal stuffiness.

Dose related postural hypotension may occur, particularly in the elderly and after intramuscular injections.

Other dose-related anticholinergic-type side effects include blurring of the vision, tachycardia, constipation, and urinary hesitancy or retention.

Chlorpromazine may impair alertness, especially at the start of the treatment. These effects may be potentiated by alcohol.

Extrapyramidal reactions in the form of acute dystonias, parkinsonian rigidity, tremor or akinesia, akathisia and oculogyric crises may occur, and are common on moderate to high dosage.

Tardive dyskinesia may occur during administration or following withdrawal of Chlorpromazine and other neuroleptic drugs. This syndrome is common among patients treated with moderate to high doses of antipsychotic drugs for prolonged periods of time and may prove irreversible, particularly in patients over the age of 50. It is unlikely to occur in the short-term when low or moderate doses of chlorpromazine are used as recommended, but since its occurrence may be related to duration of treatment as well as daily dose, chlorpromazine should given in the minimal effective dose for the minimum possible time, unless it is established that long-term administration for the treatment of schizophrenia is required. The potential seriousness and unpredictability of tardive dyskinesia and the fact that it has occasionally been reported to occur when neuroleptic antipsychotic drugs have been prescribed for relatively short periods in low dosage means that the prescribing of such agents requires especially careful assessment of risks versus benefit. Tardive dyskinesia can be precipitated or aggravated by anti-Parkinson drugs. Short-lived dyskinesias may occur after abrupt drug withdrawal. In schizophrenia, the response to antipsychotic drug treatment may be delayed. If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months. Neuroleptic malignant syndrome is rare but may occur with any neuroleptic.

Chlorpromazine, even in low dosage in susceptible (especially non-psychotic) individuals, may cause unpleasant subjective feelings of being mentally dulled or slowed down, nausea, dizziness, headache, or paradoxic effects of excitement, agitation, or insomnia. Confusional states or epileptic fits can occur. The effects of chlorpromazine on the heart are dose related. ECG changes, with prolongation of the QT interval and T-wave changes have been commonly reported in patients treated with moderate to high dosage; they are reversible on reducing the
dose. In a small number of cases, they have been reported to precede serious arrhythmias, including ventricular tachycardia and fibrillation, which have occurred after overdosage.

Further adverse effects are class effects of neuroleptics and can include cardiac arrest, Torsades de pointes and sudden unexplained death.

Although the mechanism is not known, a 3-fold increased risk of cerebrovascular adverse events has been seen with some atypical antipsychotics in clinical trials. This increased risk cannot be excluded for Chlorpromazine.

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia which may cause galactorrhoea, gynaecomastia and oligo- or amenorrhoea.

Sexual function, including erection and ejaculation is sometimes impaired by chlorpromazine. Weight gain is common.

Oedema has been reported. These effects may be prevented by reduction in dosage. Raised serum cholesterol and, rarely, hyperglycaemia have been reported in association with phenothiazines.

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

Pregnancy, puerperium and perinatal conditions.
Drug withdrawal syndrome neonatal (see 4.6) – frequency not known.

4.9 Overdose

Symptoms of chlorpromazine overdosage 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. 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 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 use of adrenaline. Cardiac monitoring should be immediately instituted and continued for at least 48 hours. Ventricular or supraventricular tachyarrhythmia’s usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life threatening, appropriate antiarrhythmic therapy may be considered. Avoid lignocaine and, as far as possible, long acting antiarhythmic drugs.

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

Chlorpromazine has depressant actions on the Central Nervous System, with alpha-adrenergic blocking and anticholinergic activities. It inhibits Dopamine and Prolactin release-inhibitory factor, thus stimulating the release of Prolactin. It increases the turnover of Dopamine in the brain.

It has anti-emetic, anti-puritic, serotonin-blocking and weak anti-histamine properties and slight ganglion blocking activity. It inhibits the heat regulating centre in the brain, and is analgesic and can relax skeletal muscle.

Due to its action on the autonomic system it produces vasodilatation, hypotension and tachycardia. Salivary and gastric secretions are reduced.

5.2 Pharmacokinetic properties

Chlorpromazine is readily absorbed in the gastro-intestinal tract. It is subject to first pass metabolism in the gut wall. It is extensively metabolised in the liver and excreted in the urine and faeces. The plasma half-life is only a few hours but it has a prolonged terminal elimination phase of up to about 3 weeks. Chlorpromazine is extensively bound to plasma proteins.

5.3 Preclinical safety data

No additional data of relevance to prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize Starch
Povidone
Sodium starch glycollate
Colloidal anhydrous silica
Magnesium stearate

In coating:
Hydroxypropylmethyl cellulose 5/6 cps 2910
Ethylcellulose 10 cps
Diethylphthalate
Titanium dioxide

6.2 Incompatibilities

Chlorpromazine can increase the central nervous system depression produced by other CNS-depressant drugs including alcohol, hypnotics, sedatives or strong analgesics.

It antagonises the action of adrenaline and other sympathomimetic agents and reverses the blood pressure lowering effects of adrenergic blocking agents such guanethidine and clonidine. It may impair the metabolism of tricyclic antidepressants, the anti-Parkinson effects of levodopa and the effects of anticonvulsants; it may possibly affect the control of diabetes,
or the action of anticoagulants. Antacids can impair absorption. Tea and coffee may prevent absorption by causing insoluble precipitates.

Undesirable anticholinergic effects can be enhanced by anti-Parkinson or other anticholinergic drugs. It may enhance the cardiac-depressant effects of quinidine, the absorption of corticosteroids and digoxin, the effect of diazoxide and of neuromuscular blocking agents. Interactions with propanolol have been reported. The possibility of interaction with lithium should be borne in mind.

Further information: Chlorpromazine is a phenothiazide with an aliphatic side-chain. Its pharmacological profile of activity includes pronounced sedative and hypotensive properties, with fairly marked anticholinergic and anti-emetic activity and a moderate tendency to cause extrapyramidal reactions.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

High density polystyrene with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane/polythene wads.

250 micron PVC glass-clear/green rigid PVC (pharmaceutical grade). 20 micron hard-tempered aluminum foil coated on the dull side with 6-7 gsm heat seal lacquer and printed on the bright side.
Packs of 28, 30, 50, 56, 60, 84, 100, 250, 500 & 1000 tablets

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Dr. Reddy’s Laboratories (UK) Ltd
6 Riverview Road
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HU17 0LD
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8. MARKETING AUTHORISATION NUMBER(S)

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