SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Chlorpromazine Hydrochloride 25mg/5ml Oral Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlorpromazine Hydrochloride 25mg/5ml

3. PHARMACEUTICAL FORM

Oral Solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Chlorpromazine is a phenothiazine neuroleptic. It is indicated in the following conditions:
- Schizophrenia and other psychoses (especially paranoid), mania and hypomania;
- In severe anxiety, psychomotor agitation, excitement and violent or dangerously impulsive behaviour. Chlorpromazine is used as an adjunct in the short term management of these conditions;
- Nausea and vomiting of terminal illness (where other drugs have failed or are not available)
- Childhood schizophrenia and autism.
- Intractable hiccups

4.2 Posology and method of administration

Posology

Dosage should be low to begin with and gradually increased under close supervision until the optimum dosage within the recommended range is reached.
Individual response and dosage requirements may vary greatly.

**Dosage for schizophrenia, other psychoses, mania, hypomania, anxiety, psychomotor agitation, excitement, violent or dangerously impulsive behaviour**

*Adults:* Initially 25mg three times daily or 75mg at bedtime increasing daily by 25mg to an effective maintenance dose. This maintenance dose is usually 70 to 300mg daily, but may be up to 1g daily in some patients.

*Children under 1 year:* Not recommended unless the need is life saving.

*Children 1 - 5 years:* 0.5mg/Kg bodyweight every 4 - 6 hours to a maximum recommended dose of 40mg daily.

*Children 6 - 12 years:* 1/3 to 1/2 the adult dose up to a maximum of 75 mg daily.

*Elderly or disabled patients:* Start with 1/3 to 1/2 the usual adult dose with a more gradual increase in dosage.

**Dosage for Intractable Hiccup**

*Adults:* 25 - 50mg tds or qds

*Children:* Not recommended/ no information available.

**Dosage for Vomiting and Nausea of Terminal Illness**

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

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

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

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

*Elderly or disabled patients:* Initially 1/3 to 1/2 the adult dose. The clinician should then use his judgement to obtain control.

**4.3. Contra-indications**

- comatose states
- severe CNS depression
- severe cardiovascular disease
- history of blood dyscrasia
- hypersensitivity to any of the constituents

**4.4 Special warnings and precautions for use**
Chlorpromazine should be used with caution in patients with cardiac arrhythmias, cardiac disease, severe respiratory disease, renal failure, Parkinson's disease, history of narrow angle glaucoma, prostatic hypertrophy, epilepsy, myasthenia gravis, phaeochromocytoma and in patients who have shown hypersensitivity to phenothiazines. Chlorpromazine should be used with caution in the elderly, particularly during very hot or very cold weather due to the risk of hyper/hypothermia. The elderly are particularly susceptible to postural hypotension.

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

Chlorpromazine should be avoided in patients with liver dysfunction, hypothyroidism, cardiac failure and agranulocytosis.

In patients with impaired liver function, regular monitoring of liver function is necessary.

During the first few months of treatment if signs of blood dyscrasia appear, regular blood counts should be carried out.

Withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid release.

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 brains disease are predisposing factors.

As with all antipsychotic drugs, chlorpromazine 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.

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

In those frequently handling preparations of phenothiazines, the greatest care must be taken to avoid contact of the drug with the skin.
An approximately 3-fold increased risk of cerebrovascular adverse events have 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. Chlorpromazine should be used with caution in patients with risk factors for stroke.

As with other drugs belonging to the therapeutic class of antipsychotics, chlorpromazine may cause QT prolongation. Persistently prolonged QT intervals may increase the risk of malignant arrhythmias. Therefore, chlorpromazine should be used with caution in susceptible individuals (with hypokalaemia, hypomagnesia or genetic predisposition) and in patients with a history of cardiovascular disorders, e.g. QT prolongation, significant bradycardia (<50 beats per minute), a recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. Concomitant treatment with other antipsychotics should be avoided (See section 4.5).

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 and preventive measures undertaken.

Concomitant use of chlorpromazine with other neuroleptics should be avoided.

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

**Excipients in the formulation**

This product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

This product contains hydroxybenzoate esters. These may cause allergic reactions (possibly delayed).
It also contains sorbitol and sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. It may have a mild laxative effect. The calorific value provided by sorbitol in the maximum daily dose of the product is 36 kcal. Each 5ml dose contains 2.25 g of sucrose. This should be taken into account in patients with diabetes mellitus. It may be harmful to teeth.

4.5. Interactions with other medicinal products and other forms of interaction

Phenothiazines may enhance the CNS depressant effect of alcohol, narcotic analgesics, anxiolytics, sedatives, hypnotics and other CNS depressants. Respiratory depression may occur. Barbiturates may reduce serum chlorpromazine concentrations.

Phenothiazines antagonise the action of adrenaline and other sympathomimetic drugs, and anti-epileptic drugs (lowering of convulsive threshold).

Phenothiazines enhance the hypotensive effect of anaesthetics, calcium channel blockers and other anti-hypertensives and trazodone. Higher dosages of chlorpromazine antagonise the hypotensive effect of adrenergic neurone blockers such as guanethidine. Severe postural hypotension occurs when chlorpromazine is administered concomitantly with ACE inhibitors.

Some neuroleptics and beta-blockers may increase the plasma concentrations of each other resulting in enhanced pharmacological effects of both drugs. Chlorpromazine and propranolol each inhibit the metabolism of the other.

Concomitant use of chlorpromazine with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Therefore concomitant use of these products is not recommended. Examples include certain antiarrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin, moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide, sertindole and haloperidol), certain antihistamines (such as terfenadine), cisapride, brettylum and certain antimalarials such as quinine and mefloquine. This list is not comprehensive.

Concurrent use of drugs causing electrolyte imbalance is not recommended. Diuretics, in particular causing hypokalaemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

Anti-cholinergic drugs may enhance the anti-cholinergic side effects of phenothiazines and inhibit their anti-psychotic effect.
Phenothiazines may impair the anti-parkinsonian effects of levodopa, bromocriptine, lisuride and pergolide.

The serum concentration of chlorpromazine is increased by anti-malarial agents.

Cimetidine has been reported to both increase and decrease the effects of chlorpromazine.

At high dosage, chlorpromazine reduces the response to hypoglycaemic agents and dosage of the latter may need increasing.

Phenothiazines may increase the risk of extrapyramidal effects with methyldopa, metirosine, tetrabenazine and lithium. The risk of neurotoxicity with lithium may also be enhanced by phenothiazines in general though combined use with chlorpromazine may lower serum concentrations of both drugs. Chlorpromazine has been reported to induce increased renal excretion of lithium.

Antacids reduce the absorption of phenothiazines and should not be used within two hours of administering the phenothiazine.

Documented adverse clinically significant interactions occur with alcohol.

The action of some drugs may be opposed by chlorpromazine; these include amphetamine and clonidine

Simultaneous administration of desferrioxamine and prochlorperazine has been observed to induce transient metabolic encephalopathy characterised by loss of consciousness for 48-72 hours. It is possible this may occur with chlorpromazine since it shares many of the pharmacological properties of prochlorperazine.

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.

4.6 Fertility, pregnancy and lactation

Chlorpromazine should not be used during pregnancy unless there are compelling reasons. Chlorpromazine crosses the placenta and may prolong labour. Possible effects on the foetus include lethargy, paradoxical hyperexcitability, tremor and low Apgar score. Reproductive studies in rodents have shown a potential for embryotoxicity and increased neonatal mortality.
Chlorpromazine should not be used during lactation. Phenothiazines are excreted in breast milk, with the potential of causing drowsiness and increased risk of tardive dyskinesia in the infant if nursing is prolonged.

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.

4.7. Effects on ability to drive and use machines

Chlorpromazine causes drowsiness, particularly at the start of treatment. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Side effects of Chlorpromazine include insomnia, nightmares, depression, agitation, dry mouth, nasal stuffiness, apathy, pallor, convulsions and hypothermia.

Hypotension, usually postural, is a common side effect and elderly or debilitated patients are more susceptible. Cardiac arrhythmias, possibly dose related, have been reported with neuroleptic therapy and include atrial arrhythmia, A-V block, ventricular tachycardia (rare), and fibrillation. Pre-disposing factors including pre-existing cardiac disease, hypokalaemia, old age and concurrent use of tricyclic antidepressants. ECG changes have been reported, including prolongation of the Q-T interval, S-T depression, T wave changes, Torsades de pointes and appearance of U waves. Sudden unexplained death and cardiac arrest have been reported.

In a small percentage of patients taking chlorpromazine, jaundice, which is usually transient, occurs and may be preceded by the sudden onset of fever after one to three weeks of treatment. Chlorpromazine-induced jaundice shares the biochemical and other characteristics of obstructive jaundice. The frequently accompanying eosinophilia indicates the allergic nature of this phenomenon. Treatment with chlorpromazine should be withdrawn if jaundice develops. Liver function may also be affected. Liver damage, sometimes fatal, has been reported rarely in patients treated with chlorpromazine.

Transitory leucopenia may occur and agranulocytosis has been reported very rarely, most often during the first three months of treatment, but occasionally later. If a patient shows signs of persistent infection, blood counts should be performed.

Extrapyramidal actions may occur with chlorpromazine. Acute dystonias or dyskinesias, which are usually transient are more common in children and young adults. They usually occur within the first four days of treatment or after increase in dosage.
Parkinsonism is more common in adults and elderly patients and usually develops after weeks or months of treatment. One or more of the characteristics of Parkinsonism may be apparent (e.g. tremor, rigidity, akinesia). Tremor is common.

Akathisia characteristically occurs after administration of large initial doses. Tardive dyskinesia may occur with chlorpromazine. The possible risk of developing this should be considered whenever an antipsychotic agent is used and the patient monitored for early signs.

The potential seriousness and unpredictability of tardive dyskinesia and the fact that occasionally, it has been reported to occur when neuroleptic antipsychotic agents have been prescribed for relatively short periods in low dosage, means that prescribing of such agents requires especially careful assessment of risks versus benefit. Tardive dyskinesia can be precipitated or aggravated by anti-parkinsonian drugs. Short lived dyskinesias may occur after abrupt drug withdrawal.

Contact sensitisation is a rare but serious complication in those who frequently handle phenothiazine preparations. Extreme care must be taken to avoid contact of the drug with the skin.

Immune system disorders: allergic phenomena such as angiodema, bronchospasm and urticaria have occurred with phenothiazines but anaphylactic reactions have been exceedingly rare. In very rare cases, treatment with chlorpromazine may be associated with systemic lupus erythematosus.

Patients treated with chlorpromazine may develop skin rashes of various kinds. Patients taking higher doses should be warned that they may develop photosensitivity and should avoid exposure to direct sunlight.

Ocular changes including corneal and lens opacities and development of a metallic greyish-mauve colouration of exposed skin, the cornea, the retina and conjunctiva have been reported in patients receiving long-term chlorpromazine therapy.

Antipsychotic agents including chlorpromazine, may cause hyperprolactinaemia, resulting in galactorrhoea, gynaecomastia and oligomenorrhoea or amenorrhoea. Impotence and weight gain may occur.

Phenothiazines have been reported to cause hyperglycaemia, hypercholesterolaemia, faecal impaction, severe paralytic ileus and megacolon.

Neuroleptic malignant syndrome characterised by hyperthermia, rigidity, autonomic dysfunction and altered consciousness may occur with any neuroleptic. Treatment involves immediate cessation of the neuroleptic and symptomatic management as appropriate.

Clinical doses of neuroleptics usually have little effect on respiration, but respiratory depression may occur in susceptible individuals.

Reproductive system and breast disorders: Priapism has been very rarely reported in patients treated with chlorpromazine.

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:
Not known: Drug withdrawal syndrome neonatal (see 4.6).

4.9 Overdose

Acute overdosage usually results in coma with shallow breathing, hypotension, hypothermia, absence of reflexes tachycardia, ECG changes and ventricular arrhythmias. Motor restlessness, hyperflexia, epileptiform convulsions and severe extrapyramidal dyskinesias may occur.

Treatment is symptomatic and supportive. If the patient is seen soon after the overdose (up to six 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.

Generalised vasodilation 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. The cardiovascular and respiratory systems should be monitored and supported. Acute hypotension should be treated with plasma expanders. If treatment with a vasopressor is necessary, the patient should be carefully monitored, particularly cardiac function. Adrenaline should not be used. Peripheral vasoconstriction agents are not generally recommended. Attention should be paid to symptoms of metabolic acidosis and delayed cardiac effects. Ventricular or supraventricular 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. Lidocaine should be avoided and, as far as possible, so should long acting anti-arrhythmics. Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. If severe dystonic reactions occur, they usually respond to procyclidine 5 - 10mg or orphenadrine 20 - 40mg IM or IV. Convulsions may be treated with intravenous diazepam. Neuroleptic malignant syndrome may be treated with dantrolene sodium together with cooling and general supportive measures. Chlorpromazine is not dialysable

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

As an antipsychotic, it is thought to improve psychotic conditions by blocking post-synaptic dopamine receptors in the brain. Also produces an alpha-
adrenergic blocking effect and depresses the release of hypothalamic, pituitary and hypophyseal hormones.

As an anti-emetic, it inhibits the medullary chemoreceptor trigger zone.

As a sedative, it is thought to cause indirect reduction of stimuli to the brain stem reticular system.

5.2. Pharmacokinetic properties

Peak plasma concentrations attained in 2 - 4 hours. The drug is highly lipophilic, highly membrane or protein bound, and accumulates in the brain, lung and other tissues with good blood supply. Pharmacokinetics follow a multiphasic pattern. The elimination half life with respect to total concentrations in plasma are typically 20 - 40 hours. Biological effects of single doses usually persist for at least 24 hours.

Elimination from plasma may be more rapid than sites of high lipid content and binding, notably the CNS.

Main route of metabolism is by oxidation, this is mediated by hepatic microsomal and other enzymes. Conjugation with glucuronic acid is prominent. Hydrophilic metabolites are excreted in urine, and to some extent in the bile.

Oral dose bioavailability: 32 +/- 19%, 95 - 98% plasma bound. Half life 30 +/- 7 hours.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Ascorbic acid (E300), sorbitol solution 70% (E420), sucrose, methyl hydroxybenzoate (E218), ethyl hydroxybenzoate (E214), propyl hydroxybenzoate (E216), propylene glycol (E1520), caramel (E150), apricot flavour, garden mint flavour, isopropyl alcohol and purified water.
6.2. **Incompatibilities**

None known.

6.3. **Shelf life**

36 months.
6 months once opened.

6.4. **Special precautions for storage**

Store below 25°C. Protect from freezing.

6.5. **Nature and contents of container**

- **Bottles:** Amber (Type III) glass.
- **Closures:** HDPE, EPE wadded, tamper evident, child resistant closure.
- **Pack size:** 150ml

6.6. **Instruction for use/handling**

Keep out of the reach of children.

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7 **MARKETING AUTHORISATION HOLDER**

Rosemont Pharmaceuticals Ltd.
Rosemont House
Yorkdale Industrial Park
Braithwaite Street
Leeds
LS11 9XE

8. **MARKETING AUTHORISATION NUMBER**

PL 0427/5017R
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY

Date of first authorisation: 30 October 1985
Date of latest renewal: 22 March 2005

10 DATE OF REVISION OF THE TEXT

26/07/2013