SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Chlorpromazine Hydrochloride 100mg/5ml Oral Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlorpromazine Hydrochloride 100mg/5ml

Excipient(s) with known effect:
Ethanol 0.37mg/5ml
Ethyl Parahydroxybenzoate (E214) 0.70mg/5ml
Methyl Parahydroxybenzoate (E218) 3.19mg/5ml
Propyl Parahydroxybenzoate (E216) 0.48mg/5ml
Propylene Glycol (E1520) 83.73mg/5ml
Sorbitol (E420) 455mg/5ml
Sucrose 2.25g/5ml

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Brown-red syrup with odour and taste of mint and apricot for oral administration.

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

For oral administration only.

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 recommended dose 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 clinical judgement to obtain control.

4.3. Contraindications

- Hypersensitivity to chlorpromazine or to any of the excipients listed in section 6.1.
- Comatose states
- Severe CNS depression
- History of blood dyscrasias including bone marrow depression and agranulocytosis.
- Severe cardiovascular disease
- Risk of angle-closure glaucoma
- Risk of urinary retention related to urethroprostatic disorders
- Dopaminergic antiparkinsonism agents (see Section 4.5)
- Nursing mothers (see Section 4.6)
- Citalopram and escitalopram

4.4 Special warnings and precautions for use

Blood disorders

All patients must be advised that, if they experience fever, sore throat or any other infection, they should inform their physician immediately and undergo a complete blood count. Treatment will be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the latter.

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: treatment must be interrupted in the event of unexplained hyperpyrexia since this can be one of the signs of neuroleptic malignant syndrome (pallor, hyperthermia, autonomic dysfunction, altered consciousness, muscle rigidity). Signs of autonomic instability, such as hyperhydrosis and irregular blood pressure, can precede the onset of hyperthermia and as such constitute premonitory signs of this syndrome. While this neuroleptic-related effect can be of idiosyncratic origin, certain risk factors such as dehydration and brain damage would seem to indicate a predisposition.

Chlorpromazine should be avoided in patients with, hypothyroidism, phaeochromocytoma, myasthenia gravis and prostate hypertrophy. It should be avoided in patients known to be hypersensitive to phenothiazines or with a history of narrow angle glaucoma or agranulocytosis.

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. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment (see Section 4.8).

Where clinically possible, the absence of any factors favouring the onset of ventricular arrhythmias should be ensured before administration:

- Bradycardia less than 55 beats per minute;
- Hypokalemia;
- Hypocalcaemia;
- Hypomagnesaemia;
- Starvation;
- Alcohol abuse;
- Concomitant therapy with other drugs known to prolong the QT interval;
- Congenital long QT interval;
- Ongoing treatment with any drug which could induce marked bradycardia (<55 beats per minute), hypokalemia, intracardiac conduction depression or QT prolongation (see Section 4.5)

With the exception of emergencies, it is recommended that the initial work up of patients receiving a neuroleptic should include an ECG.

Except under exceptional circumstances, this drug must not be administered to patients with Parkinson's disease.

The concomitant use of chlorpromazine with lithium, other QT prolonging agents, and dopaminergic antiparkinsonium agents is not recommended (see Section 4.5).

The onset of paralytic ileus, potentially indicated by abdominal bloating and pain, must be treated as an emergency (see Section 4.8).

Cases of venous thromboembolism (VTE), sometimes fatal 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 preventative measures undertaken.

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

Elderly Patients with Dementia: Elderly patients with dementia-related psychosis treated with antipsychotics drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (eg., heart failure, sudden death) or infectious (eg. , pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

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.

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

Because of the risk of photosensitisation, patients should be advised to avoid exposure to direct sunlight (see Section 4.8).

In those frequently handling preparations of phenothiazines, the greatest care must be taken to avoid contact of the drug with the skin.

Hyperglycaemia or intolerance to glucose has been reported in patients treated with chlorpromazine. Patients with established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on chlorpromazine, should get appropriate glycaemic monitoring during treatment (see section 4.8).

Severe liver toxicity
Severe liver toxicity, resulting sometimes in death, has been reported with chlorpromazine use. Patients or caregivers should immediately report signs and symptoms such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a physician. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately (see section 4.8).

Eosinophilia
The presence of eosinophilia may indicate an allergic reaction to chlorpromazine. A thorough clinical examination and a repeat complete blood count (CBC) with differential count to confirm the presence of eosinophilia should be performed (see section 4.8).

Drug reaction with eosinophilia and systemic symptoms

Drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal, have been reported in association with chlorpromazine treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, chlorpromazine should be withdrawn immediately and not be restarted

The following populations must be closely monitored after administration of chlorpromazine:

- Epileptics, since chlorpromazine may lower the seizure threshold. Treatment must be discontinued if seizures occur.
- Elderly patients presenting with heightened susceptibility to orthostatic hypotension, sedation and extrapyramidal effects; chronic constipation (risk of paralytic ileus), and potentially prostatic hypertrophy. It should be used with caution particularly during very hot or cold weather (risk of hyper-, hypothermia
- Patients presenting with certain forms of cardiovascular disease, since this class of drug has quinidine–like effects can induce tachycardia and hypotension.
- Patients with severe liver and/or renal failure because of the risk of accumulation.
- Patients on long-term treatment should receive regular ophthalmological and haematological examinations.
- Patients are strongly advised not to consume alcohol and alcohol-containing drugs throughout treatment (see Section 4.5)
- Owing to the risk of hypotension, patients should be advised to remain supine for at least half an hour after injection. Tachycardia as well as local pain or nodule formation may occur after intramuscular administration. Blood pressure should be monitored when receiving parenteral chlorpromazine
- Risk of allergic reaction including anaphylactic reactions and bronchospasm owing to the presence of sodium sulfite and disulfite in the formulation.
- Since there is a potential impact on cognitive function, children should undergo a yearly clinical examination to evaluate learning capacity. The dosage should be adjusted regularly as a function of the clinical status of the child.
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Excipient Warnings

This product contains:

- Ethanol – This medicine contains 0.37mg of alcohol (ethanol) in each 5ml. The amount in 5ml of this medicine is equivalent to less than 1ml beer and 1ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.
- Methyl, Ethyl and Propyl hydroxybenzoates (E218, E214, and E216) – May cause allergic reactions (possibly delayed).
- Propylene Glycol (E1520) – This medicine contains 83.73mg of propylene glycol in each 5ml.
- Sorbitol (E420) – This medicine contains 455mg sorbitol in each 5ml. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered

concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

- Sucrose – This medicine contains 2.25g of sucrose in each 5ml. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth.

4.5 Interaction with other medicinal products and other forms of interaction

Adrenaline must not be used in patients overdosed with chlorpromazine.

Anticholinergic drugs may reduce the antipsychotic effect of chlorpromazine and the mild anticholinergic effect of chlorpromazine may be enhanced by other anticholinergic drugs possibly leading to constipation, heat stroke, etc.

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

Increases or decreases in the plasma concentrations of a number of drugs, e.g. propranolol, phenobarbital have been observed but were not of clinical significance.

Simultaneous administration of deferoxamine and prochlorperazine has been observed to induce a 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.

<u>Combinations contraindicated</u>

Dopaminergics (quinaglide, cabergoline), not including dopaminergic antiparkinsonism agents, are contraindicated (see Section 4.3); reciprocal antagonism of the dopaminergic agent and neuroleptic.

Citalopram and escitalopram are contraindicated.

<u>Combinations not recommended</u>

Dopaminergic antiparkinsonium agents (amantadine, bromocriptine, cabergoline, levodopa, lisuride, pergolide, piribedil, ropinirole) are not recommended: reciprocal antagonism of the antiparkinsonism agent and neuroleptic (see Section 4.4). Neuroleptic-induced extrapyramidal syndrome should be treated with an anticholinergic rather than a dopaminergic anti-parkinsonism agent (dopaminergic receptors blocked by neuroleptics).

Levodopa: reciprocal antagonism of levodopa and the neuroleptic. In Parkinson's patients, it is recommended to use the minimal doses of each drug.

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

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

QT prolonging drugs: There is an increased risk of arrhythmias when neuroleptics are used with concomitant QT prolonging drugs (including certain antiarrhythmics, antidepressants and other antipsychotics including sultopride) and drugs causing electrolyte imbalance.(see Section 4.4) Diuretics, in particular causing hypokalaemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred.

Alcohol: alcohol potentiates the sedative effect of neuroleptics. Changes in alertness can make it dangerous to drive or operate machinery. Alcoholic beverages and medication containing alcohol should be avoided (see section 4.4)

Lithium (high doses of neuroleptics): concomitant use can cause confusional syndrome, hypertonia and hyper-reflexivity, occasionally with a rapid increase in serum concentrations of lithium (see Section 4.4). There have been rare cases of neurotoxicity. Lithium can interfere with the absorption of neuroleptic agents.

Combinations requiring precautions

Anti-diabetic agents: concomitant administration of high chlorpromazine doses (100mg/day) and anti-diabetic agents can lead to an increase in blood sugar levels (decreased insulin release). Forewarn the patient and advise increased self-monitoring of blood and urine levels. If necessary, adjust the anti-diabetic dosage during and after discontinuing neuroleptic treatment.

Topical gastrointestinal agents (magnesium, aluminium and calcium salts, oxides and hydroxides): decreased GI absorption of phenothiazine neuroleptics. Do not administer phenothiazine neuroleptics simultaneously with topical GI agents (administer more than 2 hours apart if possible).

CYP1A2 inhibitors

Administration of chlorpromazine with CYP1A2 inhibitors, in particular strong or moderate inhibitors may lead to an increase of chlorpromazine plasma concentrations. Therefore patients may experience a chlorpromazine dose-dependent adverse drug reaction.

There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates.

Combinations to be taken into consideration

Antihypertensive agents: potentiation of the antihypertensive effect and risk of orthostatic hypotension (additive effects). Guanethidine has adverse clinically significant interactions documented. Phenothiazines enhance the hypotensive effect of anaesthetics, calcium channel blockers, trazodone and other anti-hypertensives. Severe postural hypotension may occur with concomitant administration of chlorpromazine and ACE inhibitors.

Atropine and other atropine derivatives: imipramine, antidepressants, histamine H1-receptor antagonists, anticholinergic antiparkinsonism agents, atropinic

antispasmodics, dispyramide: build-up of atropine-associated adverse effects such as urinary retention, constipation and dry mouth, heat stroke etc.

Other CNS depressants: morphine derivatives (analgesics, antitussives and substitution treatments), barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, hypnotics, sedative antidepressants, histamine H1 receptor antagonists, central antihypertensive agents increased central depression. Respiratory depression may occur. Changes in alertness can make it dangerous to drive or operate machinery.

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

4.6. Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence of the safety of chlorpromazine in human pregnancy. 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 3-4 cm. Possible adverse effects on the foetus include lethargy or paradoxical hyperexcitability, tremor and low Apgar score.

A large amount of exposure to chlorpromazine during pregnancy did not reveal any teratogenic effect.

It is advised to keep an adequate maternal psychic balance during pregnancy in order to avoid decompensation. If a treatment is necessary to ensure this balance, the treatment should be started or continued at effective dose all through pregnancy.

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, bradycardia, tachycardia, feeding disorder, meconium ileus, delayed meconium passage, abdominal bloating. Consequently, newborns should be monitored carefully in order to plan appropriate treatment.

Lactation

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.

Fertility

A decrease in fertility was observed in female animals treated with chlorpromazine. In male animals data are insufficient to assess fertility.

In humans, because of the interaction with dopamine receptors, chlorpromazine may cause hyperprolactinaemia which can be associated with impaired fertility in women (see section 4.8). In men, data on consequences of hyperprolactinaemia are insufficient with regard to fertility.

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

System Organ Class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Not known (cannot be estimated from available data)
Blood and lymphatic system disorders			Agranulocytosis Leucopenia Eosinophilia Thrombocytopenia
Immune system disorders			Systemic lupus erythematosus Antinuclear antibody positive[1] Bronchospasm Anaphylactic reactions
Endocrine disorders		Hyperprolactinaemia Amenorrhoea	Galactorrhoea Gynaecomastia Erectile dysfunction Impotence Female sexual arousal disorder Oligomenorrhoea
Metabolism and nutrition disorders	Weight increased	Glucose tolerance impaired (see section 4.4)	Hyperglycaemia (see section 4.4) Hypertriglyceridaemia Hypercholesterolaemia Hyponatraemia Inappropriate antidiuretic hormone secretion
Psychiatric disorders		Anxiety	Lethargy Mood altered Nightmares Depression Apathy
Nervous system disorders	Sedation[2] Somnolence[2] Dyskinesia (Acute dystonias or dyskenias, usually transitory are more common in children and young adults and usually occur within the first 4 days of treatment or after dosage increases.) Tardive dyskinesia[3] Extrapyramidal disorder Akathisia-often after large initial dose	Hypertonia Convulsion	Torticolis Oculogyric crisis Trismus Akinesia Hyperkinesia Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) (see section 4.4) Parkinsonism (more common in adults and the elderly. It usually develops after weeks or months of treatment) to include tremor, rigidity or other features of Parkinsonism
Eye disorders			Accommodation disorder[4]

			Deposit eye[5] Ocular changes including corneal and lens opacities[7]
Cardiac disorders		ECG changes include Electrocardiogram QT prolonged (as with other neuroleptics) (see section 4.4), ST depression, U-Wave and T-Wave changes.	Cardiac arrhythmias, including Ventricular arrhythmia and atrial arrhythmias, a-v block, Ventricular fibrillation Ventricular tachycardia Torsade de pointes 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. Sudden death/ Sudden cardiac death (with possible causes of cardiac origin as well as cases of unexplained sudden death, in patients receiving neurleptic phenothiazines) (see section 4.4)
Vascular disorders	Orthostatic hypotension (Elderly or volume depleted subjects are particularly susceptible: it is more likely to occur after intramuscular administration.)		Embolism venous Pulmonary embolism (sometimes fatal) Deep vein thrombosis (see section 4.4)
Respiratory, thoracic and mediastinal disorders			Respiratory depression Nasal stuffiness
Gastrointestinal disorders	Dry mouth Constipation (see section 4.4)		Colitis ischaemic Ileus paralytic (see section 4.4) Intestinal perforation (sometimes fatal) Gastrointestinal necrosis (sometimes fatal) Necrotising colitis (sometimes fatal) Intestinal obstruction Faecal impaction Megacolon
Hepatobiliary disorders			Jaundice cholestatic[6] Hepatocellular Liver Injury[6] Cholestatic liver injury[6] Mixed liver injury Liver disease, sometimes fatal
Skin and subcutaneous tissue disorders			Dermatitis allergic Angioedema Contact skin sensitisation may

			occur rarely in those frequently handling preparations of chlorpromazine (see section 4.4) Skin rashes Urticaria Photosensitivity reaction
Renal and urinary disorders			Urinary retention[4]
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions			Temperature regulation disorder including hypothermia Insomnia Agitation Pallor

[1]may be seen without evidence of clinical disease
[2]particularly at the start of treatment
[3]particularly during long term treatment; may occur after the neuroleptic is withdrawn and resolve after reintroduction of treatment or if the dose is increased.
[4]linked to anticholinergic effects
[5]in the anterior segment of the eye caused by accumulation of the drug but generally without any impact on sight
[6]A premonitory sign may be a sudden onset of fever after one to three weeks of treatment followed by the development of jaundice. Chlorpromazine jaundice has the biochemical and other characteristics of obstructive (cholestatic) jaundice and is associated with obstructions of the canaliculi by bile thrombi; the frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Liver injury, sometimes fatal, has been reported rarely in patients treated with chlorpromazine. Treatment should be withheld on the development of jaundice (see section 4.4).
[7]The development of a metallic greyish-mauve coloration of exposed skin, the cornea, retina and conjunctiva has been noted in some individuals, mainly females, who have received chlorpromazine continuously for long periods (four to eight years)

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

Acute overdosage usually results in drowsiness or loss of consciousness, coma with shallow breathing, parkinsonism, hypotension, hypothermia, absence of reflexes

tachycardia, ECG changes and ventricular arrhythmias. Motor restlessness, hyperflexia, epileptiform convulsions and severe extrapyramidal dyskinesias may occur.

Treatment should be symptomatic with continuous respiratory and cardiac monitoring (risk of prolonged QT interval) until the patient's conditions resolves.

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. Treatment is supportive. Positive inotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse.

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 tachyarrhythmias 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

Pharmacotherapeutic Group: Antipsychotics, ATC Code: N05AA01

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 accumulate 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 availability: 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

Isopropyl alcohol 60%v/v, caramel (E150), methyl hydroxybenzoate (E218), ethyl hydroxybenzoate (E214), propyl hydroxybenzoate (E216), propylene glycol (E1520), sucrose, sorbitol solution 70% (E420), apricot flavour (contains ethanol), garden mint flavour (contains propylene glycol), ascorbic acid (E300) and purified water.

6.2. Incompatibilities

None known.

6.3. Shelf life

24 months- unopened.
6 months after opening.

6.4. Special precautions for storage

Store below 25°C and protect from light and freezing.

6.5. Nature and contents of container

Bottles:	- Amber (type III) glass.
Closures:	a) Aluminium, EPE wadded, roll-on pilfer-proof (ROPP) screw cap. b) HDPE, EPE wadded, tamper evident screw cap. c) HDPE, EPE wadded, tamper evident, child resistant closure.
Pack sizes:	150ml, 200ml and 500ml.

6.6 Special precautions for disposal

Keep out of the reach of children

7 MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 00427/0072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 July 1986

Date of latest renewal: 22 March 2005

10 DATE OF REVISION OF THE TEXT

13/07/2023