SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Chlorpromazine 25 mg/5 ml Solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlorpromazine solution contains 0.5% w/v Chlorpromazine Hydrochloride (25mg Chlorpromazine Hydrochloride in 5ml).

Excipients with known effect
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Solution

Chlorpromazine solution is a clear orange colour.

4.1 Therapeutic indications

Chlorpromazine is a phenothiazine neuroleptic. It is indicated in the following conditions:

- Schizophrenia, other psychoses (especially paranoid) mania and hypomania.
- Anxiety, psychomotor agitation, excitement, violent or dangerously impulsive behaviour. Chlorpromazine is used as an adjunct in the short term treatment of these conditions.
- Intractable hiccup.
- Nausea and vomiting of terminal illness (where other drugs are not available).
- Childhood schizophrenia and autism.

4.2 Posology and method of administration

Method of administration
For oral administration. Initial dosage should be low and gradually increased until the optimal dosage for the patient is achieved. Patients should be under close supervision at the start of treatment until their optimal dosage has been reached. Individual patient dosage varies considerably and the optimum dosage may vary according to the formulation.

Posology

Dosage of Chlorpromazine in:

Schizophrenia, other psychoses, anxiety, childhood schizophrenia and autism

Adult	**Children under 1 year**	**Children 1- under 6 years**	**Children 6-12 years**	**Elderly or debilitated patients**
Initially 25mg three time a day or 75mg at bedtime increasing the daily amounts of 25mg to an effective maintenance dose. This is usually between 75mg and 300mg daily, but some patients may require up to 1g per day.	Do not use unless need is life saving.	0.5mg/kg bodyweight every 4-6 hours to a maximum recommended dose of 40mg daily.	1/3 to ½ of adult dose /to a maximum recommended daily dose of 75mg.	Start with 1/3 to ½ of the usual adult dose with a more gradual increase in dosage.
Hiccup				
Adult	**Children under 1 year**	**Children 1- under 6 years**	**Children 6-12 years**	**Elderly or debilitated patients**
25 –50mg three times a day or four times a day	No information available	No information available	No information available	No information available
NAUSEA AND VOMITING OF TERMINAL ILLNESS				
Adults	**Children under 1 year**	**Children 1 – under 6 years**	**Children 6-12 years**	**Elderly or debilitated patients**
10-25mg every 4-6 hours	Do not use unless need is life saving	0.5mg/kg of bodyweight every 4-6 hours. Maximum daily dosage should not exceed	0.5mg/kg of bodyweight every 4-6 hours. Maximum daily dose should not exceed 75mg.	Initially ⅓ to ½ the adult dose. The physician should then use his clinical judgement to obtain control.

		40mg		

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Bone marrow depression
- Risk of angle-closure glaucoma
- Risk of urinary retention related to urethroprostatic disorders
- History of agranylocytosis
- Dopaminergic antiparkinsonism agents (see Section 4.5)
- Nursing mothers (see Section 4.6)
- Citalopram, escitalopram

4.4 Special warnings and precautions for use

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 neurolepticrelated 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.

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.

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 and 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 (e.g., 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).

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)

• Risk of allergic reaction including anaphylactic reactions and bronchospasm owing to the presence of sodium sulphite 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.

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.

Combinations not recommended

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 antiparkinsonism 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.

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)

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 selfmonitoring 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).

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.

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. Changes in alertness can make it dangerous to drive or operate machinery.

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 Chrorpromazine) 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 may be excreted in milk, therefore breastfeeding should be suspended during treatment.

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

Drowsiness may occur during the initial days of treatment, therefore patients should be warned not to drive or operate machinery until these effects have ceased.

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
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
Metabolism and nutrition disorders	Weight increased	Glucose tolerance impaired (see section 4.4)	Hyperglycaemia (see section 4.4) Hypertriglyceridaemia Hyponatraemia Inappropriate antidiuretic hormone secretion
Psychiatric disorders		Anxiety	Lethargy Mood altered
Nervous system disorders	Sedation[2] Somnolence[2] Dyskinesia (Acute dystonias or dyskenias, usually transitory are more common in children and	Hypertonia Convulsion	Torticollis Oculogyric crisis Trismus Akinesia Hyperkinesia Neuroleptic malignant Syndrome (hyperthermia, rigidity, autonomic dysfunction 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		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[7]
Cardiac disorders		ECG changes include Electrocadiogram 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 arrests 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
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
Hepatobiliary disorders			Jaundice cholestatic[6] Liver Injury[6] Cholestatic liver injury[6] Mixed liver injury
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,			Drug withdrawal

puerperium and Perinatal conditions			syndrome neonatal (see section 4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions			Temperature regulation disorder Insomnia Agitation

[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 has been noted in some individuals, mainly females, who have received chlorpromazine continuously for long periods (four to eight years).

Risk of allergic reactions including anaphylactic reactions and bronchospasm owing to the presence of sodium sulphite and disulfite in the formulation.

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 the Yellow Card Scheme Website :www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store.

4.9 Overdose

Toxicity and treatment of overdosage: Symptoms of chlorpromazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, ECG changes, ventricular arrhythmia's, hypothermia, Parkinsonism, convulsions and coma. Severe extra-pyramidal dyskinesias may occur.

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

If the patient is seen sufficiently soon (up to 6 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.

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.

Positive inotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstriction agents are not generally recommended; 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 lidocaine 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 (5-10mg) or orphenadrine (20-40mg) administered intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam.

Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium may be tried.

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipsychotics, ATC Code:N05A A01

Chlorpromazine is a phenothiazine neuroleptic.

5.2 Pharmacokinetic properties

Chlorpromazine is rapidly absorbed and widely distributed in the body. It is metabolised in the liver and excreted in the urine and in the bile. Although the plasma concentrations of Chlorpromazine decline rapidly the excretion of Chlorpromazine metabolites from the body is very slow. Chlorpromazine is highly bound to plasma proteins. It readily diffuses across the placental barrier and small quantities have been detected in breastmilk. Children require smaller dosages than adults.

5.3 Preclinical safety data

There is no additional preclinical safety data of relevance to the prescriber other than that already mentioned in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxyethylcellulose
Glycerol (E422)
Sorbitol 70%
Hydrochloric Acid
Aspartame
Citric Acid Monohydrate
Sunset Yellow (E110)
Polysorbate 20
Ethanol 96%
Star Anise Oil
Sodium Benzoate
Purified Water

6.2 Incompatibilities

None Stated

6.3 Shelf-Life

Shelf life of medicinal product as packaged for sale:
4 years unopened.

Shelf life after opening the container:
Once opened the solution must be used within 1 month.

6.4 Special Precautions for Storage

Do not store above 25° C. Keep container in the outer carton.

6.5 Nature and Content of Container

Packs sizes of 100ml, 150ml and 200ml.
Type III amber glass bottles or High Density Polyethylene bottles with aluminium screw cap, polypropylene tamper evident screw cap or child resistant closure.

6.6 Instructions for Use, Handling and Disposal

This solution should be handled with care as there is a risk of contact sensitization.

7. MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited, *Trading as* Pinewood Healthcare.
Ballymacarbry
Clonmel
Co. Tipperary

8. MARKETING AUTHORISATION NUMBER

PL 04917/0036

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/03/2009

10 DATE OF REVISION OF THE TEXT

08/09/2017