SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clonactil 25 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg Chlorpromazine Hydrochloride.

Excipient with known effect:
Lactose monohydrate: 71.5 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets (Tablets).

White, circular, biconvex film-coated tablet engraved with CZ1 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

(i) In the management of anxiety and tension states, agitation, depression and behavioural disturbances.
(ii) In the management of schizophrenia and other psychoses including mania and hypomania, and psychopathy, and in the control of the central effects of such drugs as LSD.
(iii) In the management of terminal illness and intractable hiccup.

4.2 Posology and method of administration

Recommended Dosage
There is a large inter and intra-individual variation in the kinetics of chlorpromazine, dosage must be on an individual basis. Initial dosage should be low and gradually increased under close supervision to the optimum level.

Anxiety, agitation & psychoses, behavioural disturbance

Adults
The recommended total daily dosage is 75 to 300 mg in divided doses, but in the management of psychoses, dosage may be as high as l g daily.

Paediatric population

6-12 years of age
$^1/_3$ to ½ the adult dose to a maximum recommended dose of 75 mg/day.

1-5 years
0.5 mg/kg every 4-6 hours to a maximum recommended dose of 40 mg/day.

Older people
10-25 mg once or twice daily is usually adequate in the control of agitated states. For other conditions, $^1/_3$ to ½ the usual adult dose with a gradual titration upwards.

Intractable Hiccup

Adults

10-25 mg 6 to 8 hourly, increasing to 25-50 mg, 6-8 hourly if necessary.

Terminal illness

Adults
10-25 mg, 4-6 hourly

Paediatric population
1-5 years: 0.5 mg/kg 4-6 hourly to a maximum of 40 mg/day
6-12 years: 0.5 mg/kg, 4-6 hourly to a maximum of 75 mg/kg.

Older people
Initially $^1/_3$ to ½ the adult dose, then gradual upward titration.

Method of administration
Oral.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clonactil is contraindicated in cases of coma due to direct central nervous system depressants such as alcohol, barbiturates and opiates.

Use in patients on concurrent therapy with other drugs potentially haemotoxic.

Use in nursing mothers.

Risk of angle-closure glaucoma.

Risk of urinary retention related to urethroprostatic disorders.

Bone marrow depression.

Hypothyroidism

Cardiac failure

Phaeochromocytoma

Myasthenia gravis

History of agranulocytosis.

Dopaminergic antiparkinsonism agents (see Section 4.5).

Citalopram, escitalopram.

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. Other blood dyscrasias including thrombocytopenia and haemolytic anaemia have occurred very rarely. 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.

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, disorders of autonomic function). Signs of autonomic instability, such as hyperhydrosis and irregular blood pressure, can precede the onset of hyperthermia and as such constitute premonitory signs of the 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.

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;
- hypokalaemia;
- congenital long QT interval;
- ongoing treatment with any drug which could induce marked bradycardia (<55 beats per minute), hypokalaemia, 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 prolongation agents, and dopaminergic antiparkinsonism agents is not recommended (see Section 4.5). 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.

Cases of venous thromboembolism (VTE) sometimes fatal, have been reported with antipsychotic drugs. Therefore chlorpromazine should be used with caution in patients with risk factors for thromboembolism (see Section 4.8).

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 patient 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 antipsychotic 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 2.65 in the placebo group. Although the cause 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 (e.g., 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 patient is not clear.

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.

Hyperglycaemia or intolerance to glucose has been reported in patients treated with Clonactil Tablets. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on Chlorpromazine Tablets 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.
- patients presenting with certain forms of cardiovascular disease, since this class of drug has quinidine-like effects and 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).

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

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

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

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

Avoid concomitant treatment with other neuroleptics (see section 4.5).

Clonactil contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Adrenaline must not be used in patients overdosed with chlorpromazine.

The CNS depressant actions of chlorpromazine and other neuroleptic agents may be intensified (additively) by alcohol, barbiturates and other sedatives. Respiratory depression may occur.

Anticholinergic agents 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 hypotensive effect of most antihypertensive drugs especially alpha adrenoceptor blocking agents may be exaggerated by chlorpromazine.

Some drugs interfere with the absorption of neuroleptic agents: antacids, antiparkinson and lithium.

When treatment for neuroleptic-induced extrapyramidal symptoms is required, anticholinergic antiparkinsonian agents should be used in preference to levodopa, since neuroleptics antagonise the antiparkinsonian action of dopaminergics.

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.

There is an increased risk of arrhythmias when neuroleptics are used concurrently with drugs which prolong the QT interval, including certain antiarrhythmics, antidepressants, other antipsychotics and drugs causing electrolyte imbalance (e.g. diuretics) (see sections 4.4 and 4.8).

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

In patients treated concurrently with neuroleptics and lithium, there have been rare reports of neurotoxicity.

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.

Documented adverse clinically significant interactions occur with alcohol, guanethidine and hypoglycaemic agents.

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

Concurrent administration of chlorpromazine with ACE inhibitors and angiotensin-II antagonists may result in severe postural hypotension.

Anaesthetics: Concurrent administration of chlorpromazine and anaesthetics may produce an enhanced hypotensive effect.

Opioid Analgesics: Opioid analgesics may enhance the sedative and hypotensive effects of chlorpromazine.

Antiepileptics: Phenothiazines, including chlorpromazine, may lower the seizure threshold. Serum levels of phenytoin may be raised or lowered by the use of chlorpromazine, and dosage adjustment may be necessary.

Antivirals: Ritonavir may increase the plasma concentration of chlorpromazine.

Metoclopramide: There is an increased risk of extrapyramidal effects if metoclopramide and phenothiazines are taken concurrently.

Tetrabenazine: There is an increased risk of extrapyramidal effects if tetrabenazine and phenothiazines are taken concurrently.

Cimetidine: Administration of cimetidine concomitantly with chlorpromazine may enhance the side effects of chlorpromazine.

4.6 Fertility, pregnancy and lactation

Pregnancy

The drug crosses the placenta. Animal studies indicate a teratogenic effect. No clear evidence of such an effect has been shown in man. Phenothiazines should only be used during pregnancy if it is considered essential by the physician.

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 the pregnancy.

Neonates exposed to antipsychotics (including Clonactil) 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 diseases, or feeding disorder. Consequently newborns should be monitored carefully.

If Clonactil is employed in labour it should be withheld until labour is established and the cervix dilated 3-4cm.

Lactation

Chlorpromazine is excreted in breast milk and use in nursing mothers is contraindicated.

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

Phenothiazines may induce drowsiness. Persons taking these drugs should not drive or operate machinery unless the drug has been shown not to interfere with physical or mental ability.

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 Leukopenia
Immune system disorders			Systemic lupus erythematosus Antinuclear antibody positive[1]
Endocrine disorders		Hyperprolactinaemia Amenorrhoea	Galactorrhoea Gynaecomastia Erectile dysfunction 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 Tardive dyskinesia[3] Extrapyramidal disorder (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) Akathisia	Hypertonia Convulsion	Torticollis Oculogyric crisis Trismus Akinesia Hyperkinesia Neuroleptic malignant syndrome (see Section 4.4.)
Eye disorders			Accommodation disorder Deposit eye[4]
Cardiac disorders		Electrocardiogram QT prolonged (see Section 4.4)	Ventricular arrhythmia Ventricular fibrillation Ventricular tachycardia Torsade de pointes Cardiac arrest Sudden death/Sudden cardiac death (with possible causes of cardiac origin as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines) (see Section 4.4)
Vascular disorders	Orthostatic hypotension		Embolism venous Pulmonary embolism (sometimes fatal) Deep vein thrombosis (see Section 4.4) Dose related postural hypotension may occur, particularly in the elderly and after intramuscular injections
Respiratory, thoracic and mediastinal disorders			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
Hepatobiliary disorders			Jaundice cholestatic Liver injury Cholestatic liver injury Mixed liver injury
Skin and subcutaneous tissue disorders			Dermatitis allergic Angioedema Urticaria Photosensitivity reaction
Renal and urinary disorders			Urinary retention (linked to anticholinergic effects)
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

[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] in the anterior segment of the eye caused by accumulation of the drug but generally without any impact on sight

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 be 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 paradoxical 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.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 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 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 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 vasoconstrictor 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 must be considered. Avoid lignocaine, 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic group: Phenothiazines with aliphatic side chains
ATC code: N05AA01

Clonactil is a phenothiazine neuroleptic.

The drug is a dopamine inhibitor and inhibits prolactin factor and has alpha-adrenergic blocking and anticholinergic activity as well as being a central nervous system depressant.

5.2 Pharmacokinetic properties

Chlorpromazine is a phenothiazine which is well absorbed but undergoes extensive first pass metabolism in the gut wall and liver with hydroxylation, oxidation and conjugation.

The drug is widely distributed and concentrates in the brain. It is strongly protein bound and eliminated in the urine and intestine as metabolites with a prolonged biphasic half-life of 3 hours and up to 12 days.

5.3 Preclinical safety data

Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Povidone
Magnesium Stearate
Maize Starch

Film-coating:
Hypromellose
Macrogol
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed.
Store in the original container in order to protect from light.

6.5 Nature and contents of container

Polypropylene tubes with low density polyethylene caps. High density polyethylene film may be used as packing material.

Pack sizes: 25, 50, 100, 250, 500 and 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co Tipperary

8 MARKETING AUTHORISATION NUMBER(S)

PA0126/026/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 April 1987

Date of last renewal: 8 April 2007

10 DATE OF REVISION OF THE TEXT

November 2019