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.

4.4 Special warnings and precautions for use

Clonactil tablets should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis, prostate hypertrophy. It should be avoided in patients known to be hypersensitive to phenothiazines or with a history of narrow angle glaucoma or agranulocytosis. It should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper-, hypothermia). The elderly are particularly susceptible to postural hypotension.

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.

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

Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) 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.

Prolonged administration of any phenothiazine may result in persistent or tardive dyskinesias, particularly in the elderly.

In common with other antipsychotics chlorpromazine has been associated with persistent dyskinesia. Tardive dyskinesia may develop in some patients on long term therapy, possibly in relation to total cumulative dose, or may develop after drug therapy has been discontinued. The risk is reported to be greater in elderly patients on high dose therapy.

Characteristic symptoms are rhythmical involuntary movements of the tongue, face, mouth or jaw sometimes accompanied by involuntary movements of the extremities. They persist for many months or even years and, while they gradually disappear in some patients, they appear to be permanent in others.

At the first signs of tardive dyskinesia which may be orofacial dyskinesia the benefit of continued treatment should be carefully assessed against the risk of the development of persistent dyskinesia. Withdrawal of treatment with careful observation of the dyskinesia and psychotic condition has been suggested in order to assess the need for continued neuroleptic therapy and to reveal persisting dyskinesia. Should it be necessary to reinstate treatment, the antipsychotic agent may mask the syndrome. Antiparkinsonian agents have proved of little value in this syndrome.

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. The risk-benefit should be fully addressed before Chlorpromazine treatment is commenced. If the clinical situation permits, medical and laboratory evaluations (e.g. biochemical status and ECG) should be performed to rule out possible risk factors (e.g. cardiac disease; family history of QT prolongation, metabolic abnormalities such as hypokalaemia, hypocalcaemia or hypomagnesaemia; starvation; alcohol abuse; concomitant therapy with other drugs known to prolong the QT interval) before initiating treatment with Chlorpromazine and during the initial phase of treatment, or as deemed necessary during the treatment (see also sections 4.4 and 4.8).

It is imperative that treatment is 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 brain 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 (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.

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.

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.

Increased Mortality in Older people with Dementia

Data from two large observational studies showed that older 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.

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, the Lapp 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

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.

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.

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

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

Autonomic disturbances:

- Postural hypotension.

- Anticholinergic effects such as dry mouth, accommodation disorders, risk of urinary retention, constipation and even paralytic ileus (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE).

Neuropsychiatric disorders:

- Sedation or drowsiness, particularly at the start of treatment.

Endocrine and metabolic reactions:

- Hyperprolactinemia: amenorrhea, galactorrhea, gynecomastia, impotence, frigidity.
- Thermoregulation disorders.
- Weight gain.
- Hyperglycemia, changes in glucose tolerance.

Cardiac disorders:

- Tachycardia
- Cardiac arrest
- QT interval prolongation.
- Very rare cases of torsades de pointes have been reported.
- Very rare cases of ventricular arrythmias (VF, VT) have been reported.

Vascular disorders:

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

Skin reactions:

- Allergic skin reactions, rash
- Photosensitivity.

Hematological disorders:

- Exceptionally agranulocytosis, regular blood counts are recommended.
- Leucocytopenia.

Pregnancy, puerperium and perinatal conditions:

- Drug withdrawal syndrome neonatal (see Section 4.6) – frequency not known.

Miscellaneous:

- Cholestatic jaundice and liver injury, mainly of cholestatic or mixed type, are rarely reported in patients treated with chlorpromazine.
- Neuroleptic malignant syndrome (see SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE).
- Priapism has been very rarely reported in patients treated with chlorpromazine.
- Drowsiness
- Agitation
- Insomnia
- Nasal congestion

Sudden, unexpected and unexplained deaths have been reported in hospitalised psychotic patients receiving phenothiazines.

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

<u>Film-coating:</u>
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

August 2016