SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Chlorpromazine 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of Chlorpromazine Hydrochloride Ph.Eur.
Excipient: Lactose monohydrate 160 mg and sucrose 62 mg
For full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet.

Appearance:
White, circular, biconvex, sugar-coated tablet printed with the Clonmel logo,
or
Unprinted tablets,
or
Printed with 1124 and APS logo,
or
Printed with 7H1.

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 anxiety psychomotor agitation excitement, violent or dangerously impulsive behaviour.
• Chlorpromazine is used as an adjunct in the short-term management of these conditions.
• Intractable hiccup.
• Nausea and vomiting of terminal illness (where other drugs have failed or are not available).
• Childhood schizophrenia.

4.2. Posology and Method of Administration

Dosages should be low to begin with and gradually increased under close supervision until the optimum dosage for the individual is reached.

Schizophrenia, other psychoses, anxiety and agitation

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

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

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

Children 6 - 12 years: One third to half the adult dose to a maximum recommended dose of 75 mg daily.

Elderly or debilitated patients: Start with one third to half the usual adult dose, with a more gradual increase in dosage.

Hiccups

Adults: 25 - 50 mg three or four times a day.

Nausea and vomiting of terminal illness

Adults: 10 - 25 mg every 4 to 6 hours.

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

Children 1 - 5 years: 0.5 mg/kg bodyweight every 4 to 6 hours. The maximum daily dosage should not exceed 40 mg.

Children 6 - 12 years: 0.5 mg/kg bodyweight every 4 to 6 hours. The maximum daily dosage should not exceed 75 mg.

Elderly or debilitated patients: Initially one third to half the adult dose. The physician should then use his clinical judgement to obtain control.
Administration

Oral: The tablets should be swallowed with a drink of water.

4.3 Contraindications

Chlorpromazine tablets are contra-indicated in cases of coma due to direct central nervous depressants, such as alcohol, barbiturates and opiates, hypersensitivity to chlorpromazine, bone marrow depression.

4.4 Special warnings and precautions for use

Chlorpromazine 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.

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

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 below), and requires immediate haematological investigation.

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.

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.

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).

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 Elderly people with Dementia**

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

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

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

Chlorpromazine contains lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose intolerance, fructose intolerance, sucrose-isomaltase insufficiency, 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.

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

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

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.

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

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

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 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.

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).

There is an increased risk of agranulocytosis when neuroleptics are used concurrently with drugs with myelosuppressive potential, such as carbamazepine or certain antibiotics and cytotoxics.

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

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.

*Sibutramine:* The concomitant use of phenothiazines and sibutramine should be avoided as there is an increased risk of CNS toxicity.

*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

There is inadequate evidence of the safety of chlorpromazine in human pregnancy but it has been widely used for many years without apparent ill consequence. 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 neonate include lethargy or paradoxical hyperexcitability with low Apgar score.

Neonates exposed to antipsychotics (including chlorpromazine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

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

4.7 Effects on Ability to Drive and Use Machines

Patients should be warned about drowsiness during the early days of treatment and advised not to drive or to operate machinery.

4.8 Undesirable effects

Generally adverse reactions occur at low frequency; the most common reported adverse reactions are nervous system disorders.
**Blood and lymphatic system disorders:** A mild leucopenia occurs in up to 30% of patients on prolonged high dosage. Agranulocytosis may occur rarely; it is not dose related. The occurrence of unexplained infections or fever requires immediate haematological investigation.

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

**Endocrine:** Hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea, impotence.

**Nervous system disorders:** Acute dystonias or dyskinesias, usually transitory are more common in children and young adults, and usually occur within the first 4 days of treatment or after dosage increases. Akathisia characteristically occurs after large initial doses.

Parkinsonism is more common in adults and the elderly. It usually develops after weeks or months of treatment. One or more of the following may be seen: tremor, rigidity, akinesia or other features of Parkinsonism. Commonly just tremor.

**Tardive dyskinesia:** If this occurs it is usually, but not necessarily, after prolonged or high dosage. It can even occur after treatment has been stopped. Dosage should therefore be kept low whenever possible.

Insomnia and agitation may occur.

**Skin and eyes:** Contact skin sensitisation is a serious but rare complication in those frequently handling preparations of chlorpromazine; the greatest care must be taken to avoid contact of the drug with the skin. Skin rashes of various kinds may also be seen in patients treated with the drug. Patients on high dosage should be warned that they may develop photosensitivity in sunny weather and should avoid exposure to direct sunlight.

Ocular changes and the development of a metallic greyish-mauve coloration of exposed skin have been noted in some individuals, mainly females, who have received chlorpromazine continuously for long periods (four to eight years).

**Cardiac disorders:** ECG changes include QT prolongation (as with other neuroleptics), ST depression, U-Wave and T-Wave changes. Cardiac arrhythmias, including ventricular arrhythmias and atrial arrhythmias, a-v block, ventricular tachycardia, which may result in ventricular fibrillation or 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.

There have been isolated reports of sudden death, with possible causes of cardiac origin (see section 4.4, above), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

**Vascular disorders:** Hypotension, usually postural, commonly occurs. Elderly or volume depleted subjects are particularly susceptible; it is more likely to occur after intramuscular administration.

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

**Gastrointestinal disorders:** dry mouth may occur.
**Respiratory, thoracic and mediastinal disorders:** Respiratory depression is possible in susceptible patients. Nasal stuffiness may occur.

**Hepato-biliary disorders:** Jaundice, usually transient, occurs in a very small percentage of patients taking chlorpromazine. 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 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, above)).

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

**General disorders:** Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) may occur with any neuroleptic (see section 4.4, above).

**Pregnancy, puerperium and perinatal conditions:** Drug withdrawal syndrome neonatal (see 4.6) – frequency not known.

### 4.9 Overdose

Toxicity and treatment of overdosage: Symptoms of chlorpromazine overdose include drowsiness or loss of consciousness, hypotension, tachycardia, ECG 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 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 vasoconstrictor agents are not generally recommended; avoid the use of adrenaline.

Ventricular or supraventricular tachy-arrythmias 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 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 - 10 mg) or orphenedrine (20 - 40 mg) 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

Pharmacotherapeutic Group: Phenothiazines with aliphatic side-chain
ATC Code: N0A55

The action of chlorpromazine and other neuroleptic drugs on psychiatric patients differs from classical CNS depressants such as general anaesthetics, sedatives and hypnotics and opioids. The neuroleptic syndrome consists of suppression of spontaneous movements and complex behaviour, while spinal reflexes and unconditioned nociceptive-avoidance behaviours remain intact. In man the neuroleptic drugs reduce initiative and interest in the environment and they reduce displays of emotion or affection. Initially there may be some slowness in response to external stimuli and drowsiness. However, subjects are easily aroused, capable of giving appropriate answers to direct questions and seem to have intact intellectual functions: there is no ataxia, incoordination or dysarthria at ordinary doses. Psychotic patients become less agitated and restless and withdrawn or autistic patients sometimes become more responsive and communicative. Aggressive and impulsive behaviour diminishes. Gradually (usually over a period of days) psychotic symptoms of hallucinations, delusions and disorganised or incoherent thinking tend to disappear.

5.2 Pharmacokinetic properties

Chlorpromazine is rapidly absorbed and widely distributed in the body. Chlorpromazine is extensively metabolised in the liver by sulphoxidation, N-demethylation, hydroxylation, N-oxidation, glucuronic acid conjugation and possible ring fission. Bioavailability is about 20 to 30% reduced during chronic therapy. A large number of metabolites have been isolated and some of the metabolites are active, particularly 7-hydroxychlorpromazine although less so than the parent drug. Several metabolites may be detected in plasma at concentrations similar to those of chlorpromazine during chronic treatment.

Chlorpromazine is excreted in the urine and bile. About 20 to 70% of an oral dose is excreted in the urine as metabolites, mostly conjugated, with 5% of the dose as the sulphoxide and less than 1% as unchanged drug. About 5% of a dose is eliminated in the faeces as metabolites. Whilst plasma concentration of chlorpromazine itself rapidly declines excretion of chlorpromazine metabolites is very slow. Chlorpromazine metabolites have been detected in
urine up to 18 months after discontinuation of long term treatment. The monodesmethyl, 7-hydroxy and sulphoxide metabolites are taken up by erythrocytes along with traces of the parent drug and its N-oxide. Plasma half life is 7 to 120 hours. Mean values are usually in the range 15 - 30 hours. Protein binding in plasma is 95 - 98%. It readily diffuses across the placenta. Small quantities have been detected in milk from treated women. Children require smaller dosages per kg than adults.

5.3. Pre-clinical Safety Data

No preclinical safety data submitted.

6. Pharmaceutical Particulars

6.1. List of Excipients

Lactose monohydrate, povidone, magnesium stearate, maize starch.

Sugar-coat excipients: Polyvinylacetate phthalate, stearic acid, talc, calcium carbonate, acacia, titanium dioxide (E171), sucrose, shellac, yellow carnauba wax, white beeswax.

6.2. Incompatibilities

No incompatibilities stated.

6.3. Shelf Life

1. Polypropylene tubes with low density polyethylene caps: 3 years.

2. Blister: 2 years.
6.4 Special precautions for storage

Blister
Store below 25°C.
Keep blister in the outer carton.

Polypropylene Tubes
Store below 25°C.
Store in the original tablet container.

6.5. Nature and Content of Container

1. Polypropylene tubes with low density polyethylene caps.
   Pack sizes: 25, 28, 50, 56, 100, 250, 500 and 1,000 tablets.

2. Blister (250 µm transparent PVC and 20 µm hard temper aluminium foil, in a carton).
   Pack size: 28 tablets.

6.6. Instructions for Use, Handling and Disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road
Clonmel
Co. Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER

PL 00790/0019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/01/2009

10. DATE OF REVISION OF THE TEXT

11/07/2012