1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

CHLOZINE TABLETS (Chlorpromazine Tablets BP 100 mg)

2. Qualitative and Quantitative Composition:

Each film coated tablet contains: Chlorpromazine Hydrochloride BP 100 mg

For full list of excipients see section 6.1

3. Pharmaceutical form:

White, circular, biconvex, film coated tablet.

4. Clinical particulars:

4.1 Therapeutic indications

Schizophrenia and other psychoses (especially paranoia), mania and hypomania. In anxiety, psychomotor agitation, excitement, violent or dangerously impulsive behaviour. Is used as an adjunct in the short-term management of these conditions.

Intractable hiccup.

Nausea and vomiting in terminal illness (where other drugs have failed or are not available).

Induction of hypothermia is facilitated by Chlorpromazine Tablets which prevents shivering and causes vasodilatation.

Childhood schizophrenia and autism.

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. Individuals vary considerably and the optimum dose may be affected by the formulation used.

Dosage of chlorpromazine in schizophrenia, other psychoses, anxiety and agitation etc.

Adult:

Initially 25 mg t.d.s. 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 body weight every 4-6 hours to a maximum recommended dose of 40 mg daily.

Children 6-12 years:

1/3-½ adult dose to a maximum recommended dose of 75 mg daily.

Elderly or debilitated patients:

Start with 1/3-½ usual adult dose with a more gradual increase in dosage.

Hiccups

Adult:

25-50 mg t.d.s. or q.d.s.

Children under 1 year:

No information available.

Children 1-5 years:

No information available.

Children 6-12 years:

No information available.

Elderly or debilitated patients:

As for adults.

Nausea and vomiting of terminal illness:

Adults:

10-25 mg every 4-6 hours.

Children under 1 year:

Do not use unless need is life saving.

Children 1-5 years:

0.5 mg/kg every 4-6 hours. Maximum daily dosage should not exceed 40 mg.

Children 6-12 years:

0.5 mg/kg every 4-6 hours. Maximum daily dosage should not exceed 75 mg.

Elderly or debilitated patients:

Initially 1/3-½ adult dose. The physician should then use his clinical judgment to obtain control.

Method of administration: Oral

4.3 Contraindications

- Hypothyroidism
- Cardiac failure
- Phaeochromocytoma
- Myasthenia gravis
- Hypersensitivity to chlorpromazine, phenothiazines or one of the other constituents.

• Risk of angle-closure glaucoma.
• Risk of urinary retention related to urethroprostatic disorders.
• History of agranulocytosis.
• Dopaminergic antiparkinsonism agents (see Section 4.5).
• Nursing mothers (see Section 4.6).
• Gluten allergy or intolerance (see Section 4.4).
• Citalopram, escitalopram.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 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 Tablets 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 Chlorpromazine 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.

o epileptics, since chlorpromazine may lower the seizure threshold. Treatment must be discontinued if seizures occur.

o elderly patients presenting with heightened susceptibility to orthostatic hypotension, sedation and extrapyramidal effects; chronic constipation (risk of paralytic ileus), and potentially prostatic hypertrophy.

o patients presenting with certain forms of cardiovascular disease, since this class of drug has quinidine-like effects and can induce tachycardia and hypotension.

o 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 tablets contain lactose and therefore patients with rare hereditary problems of congenital galactosemia, glucose or galactose malabsorption syndrome, lactase deficiency, galactose intolerance or the Lapp lactase deficiency should not take this medicine.

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 Tablets.

Chlorpromazine Tablets are not licenced for the treatment of dementia-related behavioural disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Combinations contraindicated</u>

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

<u>Combinations not recommended</u>

Dopaminergic antiparkinsonism 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 chlorpromazine is used with concomitant QT prolonging drugs (including certain antiarrhythmics 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 hyperreflexivity, occasionally with a rapid increase in serum concentrations of lithium (see Section 4.4).

Combinations requiring precautions

Antidiabetic agents: concomitant administration of high chlorpromazine doses (100 mg/day), and antidiabetic agents can lead to an increase in blood sugar levels (decreased insulin release). Forewarn the patient and advise increased self-monitoring of blood and urine levels. If necessary, adjust the antidiabetic 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). Phenothiazines enhance the hypotensive effect of anaesthetics and calcium channel blockers. Severe postural hypotension may occur with concomitant administration of chlorpromazine and ACE inhibitors.

Atropine and other atropine derivatives: imipramine antidepressants, histamine H1-receptor antagonists, anticholinergic, antiparkinsonism agents, atropinic antispasmodics, disopyramide: build-up of atropine-associated adverse effects such as urinary retention, constipation and dry mouth.

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

The action of some drugs may be opposed by Chlorpromazine Tablets; these include amphetamine, clonidine, guanethidine, adrenaline.

Anticholinergic agents may reduce the antipsychotic effect of Chlorpromazine Tablets. Some drugs interfere with absorption of neuroleptic agents; antacids, anti-Parkinson. Documented clinically significant adverse interactions occur with alcohol, guanethidine and hypoglycaemic agents.

4.6 Pregnancy and lactation

Pregnancy

A large amount of exposure to chlorpromazine during pregnancy did not reveal any teratogenic effect. However, there is evidence of harmful effects in animals, so 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 3-4cm.

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 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.

Lactation

Chlorpromazine being excreted in milk, breast-feeding is not recommended 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

The attention of patients, particularly drivers and machine operators, should be drawn to the risk of drowsiness with this medication especially at the start of treatment.

4.8 Undesirable effects

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Not known (cannot b estimated from availabl data)**
Blood and lymphati system disorders			Agranulocytosis Leukopenia
Immune systen disorders			Systemic lupu erythematosus Antinuclear antibody positive

Endocrine disorders		Hyperprolactinaemia Amenorrhoea	Galactorrhoea Gynaecomastia Erectile dysfunction Female sexual arousa disorder
Metabolism and nutrition disorders	Weight increased	Glucose tolerance impaired (see Section 4.4)	Hyperglycaemia (see Sectio 4.4) Hypertriglyceridaemia Hyponatraemia Inappropriate antidiureti hormone secretion
Psychiatric disorders		Anxiety	Lethargy Mood altered
Nervous system disorders	Sedation[2] Somnolence[2] Dyskinesia Tardive dyskinesia[3] Extrapyramida disorder (in the form of acute dystonias, parkinsonian rigidity, tremor or akinesia, akathisia and oculogyric crises may occur, and are common or moderate to high dosage) Akathisia	Hypertonia Convulsion	Torticollis Oculogyric crisis Trismus Akinesia Hyperkinesia Neuroleptic malignan 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/Sudde cardiac death (with possibl causes of cardiac origin a well as cases of unexplaine sudden death, in patient receiving neurolepti phenothiazines) (see Sectio 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

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.

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

If the patient is seen up to 6 hours after ingestion of a toxic dose, gastric lavage may be attempted. 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 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. Avoid use of adrenaline. Ventricular or supraventricular tachyarrhythmia's usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life threatening, appropriate antiarrhythmic therapy may be considered. Avoid lignocaine and, as far as possible, long acting antiarrhythmic drugs.

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

ATC Code: N05AA01
Pharmacotherapeutic group: Dopamine receptor antagonist

Chlorpromazine has depressant actions on the Central Nervous System, with alpha-adrenergic blocking and anticholinergic activities. It inhibits Dopamine and Prolactin release-inhibitory factor, thus stimulating the release of Prolactin. It increases the turnover of Dopamine in the brain.

It has anti-emetic, anti-puritic, serotonin-blocking and weak anti-histamine properties and slight ganglion blocking activity. It inhibits the heat regulating centre in the brain, and is analgesic and can relax skeletal muscle.

Due to its action on the autonomic system it produces vasodilatation, hypotension and tachycardia.

Salivary and gastric secretions are reduced.

5.2 Pharmacokinetic properties

Chlorpromazine is readily absorbed in the gastro-intestinal tract. It is subject to first pass metabolism in the gut wall. It is extensively metabolised in the liver and excreted

in the urine and faeces. The plasma half-life is only a few hours but it has a prolonged terminal elimination phase of up to about 3 weeks. Chlorpromazine is extensively bound to plasma proteins.

5.3 Preclinical safety data

Studies of the teratogenic and carcinogenic effects of the drug in animals have been of dubious significance. In rodents, neurological effects of exposure to phenothiazines in utero have occurred, but not with sufficient frequency to prove cause and effect. Very high doses of phenothiazines depress spermatogenesis in animals. The increase in serum prolactin concentrations (dopamine blockade of the tonic inhibitory control of release of this hormone) has been suspected of predisposing to breast cancer. An increase in mammary neoplasms has been observed in rodents after chronic exposure to antipsychotic drugs.

6. Pharmaceutical particulars:

1. List of Excipients:

Dibasic calcium phosphate	BP
Maize starch	BP
Purified talc	BP
Magnesium stearate	BP
Colloidal anhydrous silica	BP
Polyplasdone XL-10 (Crospovidone)	USPNF
Croscarmellose sodium	BP
Polacrillin potassium (Kyron T-314)	USNF

In Coating

Colour: Titanium Dioxide	Inhouse
Methylene dichloride	BP
Isopropyl alcohol	BP

List of colour ingredients

Titanium Dioxide
Hydroxyl Propyl Methyl Cellulose
Polyethylene Glycol
Talc

2. Incompatibilities:

Chlorpromazine can increase the central nervous system depression produced by other CNS-depressant drugs including alcohol, hypnotics, sedatives or strong analgesics.

It antagonises the action of adrenaline and other sympathomimetic agents and reverses the blood pressure lowering effects of adrenergic blocking agents such guanethidine and clonidine. It may impair the metabolism of tricyclic antidepressants, the anti-Parkinson effects of levodopa and the effects of anticonvulsants; it may possibly affect the control of diabetes, or the action of anticoagulants. Antacids can impair absorption. Tea and coffee may prevent absorption by causing insoluble precipitates.

Undesirable anticholinergic effects can be enhanced by anti-Parkinson or other anticholinergic drugs. It may enhance the cardiac-depressant effects of quinidine, the

absorption of corticosteroids and digoxin, the effect of diazoxide and of neuromuscular blocking agents. Interactions with propanolol have been reported. The possibility of interaction with lithium should be bone in mind.

Further information: Chlorpromazine is a phenothiazide with an aliphatic side-chain. Its pharmacological profile of activity includes pronounced sedative and hypotensive properties, with fairly marked anticholinergic and anti-emetic activity and a moderate tendency to cause extrapyramidal reactions.

6.3 Shelf-Life:

36 months from the date of manufacture.

6.4 Special Precautions for Storage:

Do not store above 30°C. Protect from light and moisture.

6.5 Nature and Contents of Container:

10 tablets packed in one Aluminium/PVC blister. Such blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

6.6 Special precautions for disposal:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Product distribution category:

POM

"Prescription Only Medicine"

7. Registrant:

AGOG PHARMA LTD.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane, India.

8. Marketing authorisation number

TAN 22 HM 0345

9. Date of first authorisation/renewal of the authorisation

21/09/2022

10. Date of revision of the text