
AUSTRALIAN PRODUCT INFORMATION – LARGACTIL (CHLORPROMAZINE HYDROCHLORIDE)

1. NAME OF THE MEDICINE

Chlorpromazine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets: Each tablet contains, 25 mg or 100 mg of chlorpromazine hydrochloride

Syrup: Each 1 mL of syrup contains 5 mg of chlorpromazine hydrochloride

Injection: The injection solution contains 50 mg/2 mL of chlorpromazine hydrochloride

List of excipients with known effect:

Tablets: Contains sugars as lactose

Syrup: Contains sugars, benzoates, sulfites and sodium

Injection: Contains sulfites

For the full list of excipients, see Section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

Tablets, Syrup, Injection Solution

Tablets

25 mg: white to off-white, circular biconvex, film-coated tablets one face impressed LG25 with the reverse side plain film coated

100 mg: white to off-white, circular biconvex, film-coated tablets one face impressed LG100 with the reverse side plain film coated

Syrup

The syrup is a clear bright, golden brown, syrupy liquid

Injection

The injection solution is a clear, bright, very pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute functional psychosis (e.g. schizophrenia, mania or psychotic depression).

Long-term treatment of schizophrenia.

Short-term treatment of agitation and severe depression.

Severe behavioural disturbances, as can be found in some children with mental retardation or autism, including the treatment of self-injurious and aggressive behaviour or overactivity. Use of chlorpromazine should be in conjunction with an appropriate non-pharmacological management program and long-term use should only be carried out under the supervision of a physician experienced in the management of psychotic disorders in children.

In the management of terminal illness to enhance the effect of analgesics and to control nausea and vomiting.

Control of intractable hiccough.

4.2 Dose and method of administration

Dosage varies with the individual and the purpose for which the drug is used, so that only general guidance can be given on the dosage likely to be effective and well tolerated. Initial dosage should be low with increases at frequent, regular intervals until the desired response has been obtained.

Adults

Sedation, hypotension and anticholinergic effects may be prominent, especially in acute administration.

Oral

A suitable initial dose for ambulant patients is 25 mg three times daily increased, if necessary, by 25 mg two or three times daily up to a total of 600mg-800mg per day. The usual maintenance doses range from 25 to 100 mg three times daily, but higher doses are sometimes used in bed patients or in psychotic cases.

LARGACTIL Syrup is intended for administration to patients who refuse tablets or have difficulty in swallowing. Crushing the tablets is not recommended, as contact of the active material with the skin should be avoided in order to minimise the risk of dermatitis.

Parenteral

Chlorpromazine injectable solutions are irritant and should be given by deep intramuscular injection, or after dilution with normal saline, by intravenous infusion. Blood pressure and vital signs should be taken before and monitored closely after injections. The usual single dose for adults is 25 to 50 mg by deep intramuscular injection and this may be repeated as necessary three to four times in 24 hours. Initial dosage of this order may sometimes cause a transient postural hypotension so that the patient should be kept under observation for the first few days of treatment. The intramuscular injection should be given in the upper outer quadrant of the buttock or upper portion of the deltoid muscle. The site should be rotated for repeated injections.

Children

Over 5 years of age, one third to one half of the appropriate adult dosage may be given; for younger children the oral dose may be calculated on the basis of 0.5 mg/kg bodyweight. This gives doses of 5 mg at 1 year, 7.5 mg at 3 years and 10 mg at 6 years. These doses may be repeated three or four times a day as necessary. Children need to be monitored for hypothermia and hypotension.

Hepatic or Renal Impairment

The dosage in these patients may need to be reduced (see Section 4.4 Special Warnings and Precautions for Use).

Elderly or Debilitated

The dosage in these patients may need to be reduced (see Section 4.4 Special Warnings and Precautions for Use).

4.3 Contraindications

Chlorpromazine should never be used in the following circumstances:

Circulatory collapse.

CNS depression, e.g. coma or drug intoxication.

Hypersensitivity to chlorpromazine, other phenothiazines, or to any of the other ingredients of Largactil.

Bone marrow depression.

Phaeochromocytoma.

Hepatic failure or active hepatic disease.

LARGACTIL Syrup contains sodium metabisulfite, sodium sulfite and sodium benzoate and LARGACTIL Injection contains sodium metabisulfite and sodium sulfite and may cause allergic-type reactions including anaphylactic symptoms and asthmatic episodes in susceptible people.

In children younger than 1 year, due to a possible association between use of phenothiazine-containing products and Sudden Infant Death Syndrome (SIDS).

4.4 Special warnings and precautions for use

Chlorpromazine generally should not be used in epilepsy, Parkinson's disease, hypoparathyroidism, myasthenia gravis and prostatic hypertrophy.

Hypersensitivity reactions including anaphylactic reaction, urticaria and angioedema have been reported with Largactil use. In case of allergic reaction, treatment with Largactil must be discontinued and appropriate symptomatic treatment initiated (see Section 4.8 Adverse Effects (Undesirable Effects)).

Largactil should be avoided in patients with liver or renal dysfunction, Parkinson's disease, hypothyroidism, cardiac failure, pheochromocytoma, myasthenia gravis, or prostate hypertrophy, or in patients with a history of narrow angle glaucoma or agranulocytosis.

Acute withdrawal symptoms, including nausea, vomiting, headache, anxiety, agitation, dyskinesia, dystonia, disturbed temperature regulation, and insomnia, have very rarely been reported following the abrupt cessation of high doses of neuroleptics. Relapse may also occur, and the emergence of extrapyramidal reactions has been reported. Therefore, gradual withdrawal is advisable. Symptoms of withdrawal can occur following treatment at any dose. Withdrawal of treatment should occur under close medical supervision.

Phenothiazines may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, general anesthetics, or alcohol.

Largactil has been associated with dystonic reactions. It should therefore be used cautiously, especially in children.

Applies only to solution for injection:

Postural hypotension with tachycardia as well as local pain or nodule formation may occur after intramuscular injection.

Oral solutions:

Because of the presence of sucrose, use of oral solutions or syrup is not recommended in patients with fructose intolerance, glucose and galactose malabsorption syndrome or sucrase-isomaltase deficiency.

Because of the presence of alcohol, these presentations are not recommended in patients with liver disease.

Epilepsy

Chlorpromazine should be avoided in patients with epilepsy as treatment with neuroleptics can result in a lowered seizure threshold. Chlorpromazine may be used in conjunction with anticonvulsant drugs.

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

Parkinson's Disease

Chlorpromazine should be avoided in parkinsonism as phenothiazines may block post synaptic dopamine receptors in the striatum. There is also a possible antagonistic effect of chlorpromazine with dopaminergic agonists used in the treatment of parkinsonism.

Hypoparathyroidism

Use of chlorpromazine should be avoided in hypoparathyroidism as a severe dystonic reaction has been reported in patients with untreated hypoparathyroidism.

Myasthenia Gravis

As the underlying defect in myasthenia gravis is a decrease in the number of available acetylcholine receptors at neuromuscular junctions, chlorpromazine should be avoided in myasthenia gravis due to its strong antimuscarinic effects.

Prostate Hypertrophy

Chlorpromazine should be avoided in patients with prostate hypertrophy due to the anticholinergic effects of phenothiazines.

Antiemetic Effects

The antiemetic effects of chlorpromazine may mask signs of overdose of toxic drugs or obscure the diagnosis of conditions such as intestinal obstruction and brain tumour.

Temperature Regulation

Phenothiazines depress the mechanism for regulation of temperature. Severe hypothermia may occur during swimming in cold water or in patients receiving antipyretic therapy, and heat stroke may occur in hot weather. Patients who develop pyrexia, along with clouding of consciousness and rigidity should cease medication and undergo immediate investigation, as these are the early symptoms of the neuroleptic malignant syndrome, a potentially lethal adverse effect of major tranquillisers (see Section 4.8 Adverse Effects (Undesirable Effects)).

Prolonged Usage

As with all phenothiazines, long term usage of chlorpromazine can cause the development of tardive dyskinesia, which may be irreversible (see Section 4.8 Adverse Effects (Undesirable Effects)).

Agranulocytosis

Agranulocytosis has been reported at an incidence of between 1:1,300 and 1:500,000. Most reported cases have occurred between the fourth and tenth week of treatment.

Warn patients to report the sudden appearance of sore throat, fever or other signs of infection. If white blood cell and differential counts indicate cellular depression, stop treatment and start antibiotic and other suitable therapy, subject to the expert guidance of a haematologist.

Retinopathy

Periodic ophthalmological examinations should be performed during prolonged therapy.

Respiratory Disease

Chlorpromazine should be used with caution in patients with chronic respiratory disorders. Chlorpromazine can suppress the cough reflex hence aspiration of vomitus is possible.

Reye's Syndrome

The extrapyramidal symptoms which can occur secondary to chlorpromazine may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g. Reye's syndrome or other encephalopathy. The use of chlorpromazine and other hepatotoxins should be avoided in children and adolescents whose signs and symptoms suggest Reye's syndrome.

Glaucoma

As with all drugs which exert an anticholinergic effect, and/or cause mydriasis, chlorpromazine should be used with caution in patients with glaucoma. As the clinical features of neuroleptic malignant syndrome include autonomic dysfunction, care should be taken when giving chlorpromazine to patients with a history of neuroleptic malignant syndrome and glaucoma. Patients should be monitored for symptoms and signs of neuroleptic malignant syndrome (see Section 4.8 Adverse Effects (Undesirable Effects)).

Photosensitivity

Because of the risk of photosensitisation, patients should be advised to avoid exposure to direct sunlight.

Patients on high doses should be warned that they may develop photosensitivity in sunny weather and should avoid exposure in strong sunlight, e.g. at the beach or snow. If exposure is unavoidable, patients should be encouraged to wear suitable clothing including a hat and to apply a SPF 15+ sunscreen. The tendency to this adverse effect may be increased with chronic dosing. Periodic examinations for lens opacities and abnormal pigmentation are required.

Hypotension

Chlorpromazine should be used with extreme caution in patients with cardiovascular disease, phaeochromocytoma, or other conditions in which a sudden drop in blood pressure would be undesirable; if it is used in conjunction with other drugs likely to cause postural hypotension, an adjustment of dosage may be necessary. Avoid adrenaline in the treatment of phenothiazine induced hypotension, as the action of adrenaline may be reversed causing a further fall in blood pressure.

QT Intervals

Very rare cases of QT interval prolongation have been reported with chlorpromazine.

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 (c). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, 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 Adverse Effects (Undesirable Effects)).

Cerebrovascular Events

An increased risk of cerebrovascular events has been reported in elderly patients with dementia treated with atypical antipsychotic drugs. An increase in the risk of cerebrovascular events with other antipsychotic drugs or other populations of patients cannot be excluded. Chlorpromazine should therefore be used with caution in patients with stroke risk factors.

Venous Thromboembolism

Cases of venous thromboembolism, 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 Adverse Effects (Undesirable Effects)).

Hyperglycemia

Hyperglycemia or intolerance to glucose has been reported in patients treated with chlorpromazine. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on chlorpromazine, should get appropriate glycemic monitoring during treatment (see Section 4.8 Adverse Effects (Undesirable Effects)).

Use in hepatic impairment

If bilirubinaemia, bilirubinuria or icterus occur, the drug should be discontinued and liver function tests performed. Routine tests are advisable during prolonged therapy. Due to the extensive hepatic metabolism and clearance of chlorpromazine, caution should be taken when treating patients with hepatic impairment. Dose reduction may be necessary in such patients.

Treatment should be discontinued immediately and another antipsychotic drug should be considered as an alternative in the following situations:

Severe liver toxicity

Severe liver toxicity, sometimes resulting in death, has been reported with chlorpromazine use. Patients or caregivers should be instructed to report immediately signs and symptoms such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a physician. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately (see Section 4.8 Adverse Effects (Undesirable Effects)).

Eosinophilia

The presence of eosinophilia may indicate an allergic reaction to chlorpromazine. A thorough clinical examination and a repeat complete blood count (CBC) with differential count to confirm the presence of eosinophilia should be performed.

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 Adverse Effects (Undesirable Effects)), and requires immediate hematological investigation.

All patients should 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 should be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the blood count.

Neuroleptic malignant syndrome

A potentially fatal syndrome called neuroleptic malignant syndrome has been reported in association with antipsychotic drugs. The syndrome is characterised by muscular rigidity, fever, hyperthermia, altered consciousness and autonomic instability (e.g. tachycardia, labile blood pressure, profuse sweating, dyspnoea).

The management of neuroleptic malignant syndrome should include immediate discontinuation of antipsychotic drugs, intensive monitoring and treatment of symptoms, and treatment of any associated medical problems.

It is imperative that treatment be 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 blood pressure 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 (see Section 4.8 Adverse Effects (Undesirable Effects)).

Prolonged administration of any phenothiazine may result in tardive dyskinesia, particularly in the elderly and children.

Tardive Dyskinesia

Tardive dyskinesia may develop in patients on antipsychotic drugs. The disorder consists of repetitive involuntary movements of the tongue, face, mouth, or jaw (e.g. protrusion of the tongue, puffing the cheeks, puckering of the mouth, chewing movements). The trunk and limbs are less frequently involved. It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of the drug increases. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses. The risk seems to be greater in elderly patients, especially females.

The syndrome may become clinically recognisable either during treatment, upon dosage reduction, or upon withdrawal of treatment. The dosage of antipsychotic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder, since the syndrome may be masked by a higher dose. In patients requiring long-term treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought.

There is no known effective treatment for tardive dyskinesia. Anti-parkinsonian agents usually do not alleviate symptoms. It is suggested that anti-psychotic agents be discontinued if symptoms of tardive dyskinesia appear.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder, and close supervision of high-risk patients should accompany therapy.

Use in renal impairment

Chlorpromazine should be given cautiously to patients with renal disease.

Alcohol use

Patients are strongly advised not to consume alcohol and alcohol-containing medicines while being treated with Largactil.

Use in the elderly

The elderly are relatively more susceptible to the adverse effects of chlorpromazine. The starting dose should be about half the usual adult dose and dosage increments should be gradual and reviewed regularly.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (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 patients is not clear.

Careful monitoring of treatment with chlorpromazine is required when administered in elderly patients exhibiting greater susceptibility to orthostatic hypotension, sedation, and extrapyramidal effects; chronic constipation (risk of ileus paralytic); possible prostatic hypertrophy.

Largactil should be used cautiously in the elderly owing to their susceptibility to drugs acting on the central nervous system and a lower initial dosage is recommended. There is an increased risk of drug-induced Parkinsonism in the elderly particularly after prolonged use.

Largactil should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper-, hypothermia).

Paediatric use

Children need to be monitored for hypothermia and hypotension (see Section 4.2 Dose and Method of Administration).

In children, because of the cognitive impact, an annual clinical examination to assess the learning capacities is recommended. The dosage will be regularly adapted based on the child's clinical condition. Use in children under 6 years of age shall be for exceptional situations in a specialized environment only.

Effects on laboratory tests

The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

4.5 Interactions with other medicines and other forms of interactions

Contraindicated combinations

Dopaminergics, except in patients with Parkinson's disease

Mutual antagonism between dopaminergics and neuroleptics. Where treatment for neuroleptic-induced extrapyramidal symptoms is required, anticholinergic antiparkinsonian agents should be used in preference to levodopa, since neuroleptics antagonize the antiparkinsonian action of dopaminergics.

Combinations not recommended or requiring precaution:

Dopaminergics in patients with Parkinson's disease

Dopaminergics may cause or exacerbate psychotic disorders. If treatment with neuroleptics is required in patients with Parkinson's disease treated with a dopaminergic, the latter should be tapered off gradually (sudden discontinuation of dopaminergic agents exposes the patient to a risk of "neuroleptic malignant syndrome"). For parkinsonian patients who require treatment with both a neuroleptic and a dopaminergic agent, use the minimum effective doses of both medications.

The action of some drugs may be opposed by phenothiazine neuroleptics; these include amphetamine, clonidine, adrenaline.

There is an increased risk of arrhythmias when antipsychotics are used with concomitant QT prolonging drugs (including certain antiarrhythmics, antidepressants and other antipsychotics) and drugs causing electrolyte imbalance.

The CNS depressant actions of neuroleptic agents may be intensified (additively) by alcohol, barbiturates and other sedatives. Respiratory depression may occur. Impaired vigilance may make it dangerous to drive or use machines. Avoid consumption of alcoholic beverages and medications containing alcohol.

Lithium: Concomitant use can increase the risk of neurotoxicity.

Interactions resulting in decreased chlorpromazine levels

Food, alcohol and benzotropine can reduce the absorption of chlorpromazine. Antacids can slow the absorption of chlorpromazine. Lithium and chronic administration of barbiturates can lead to increased clearance of chlorpromazine.

Interactions resulting in increased chlorpromazine levels

Tricyclic antidepressants decrease the clearance of chlorpromazine and may lead to increased serum levels.

Administration of chlorpromazine with CYP1A2 inhibitors, in particular strong (such as ciprofloxacin and fluvoxamine) or moderate (such as oral contraceptives, thiabendazole and vemurafenib) inhibitors, leads to an increase in chlorpromazine plasma concentrations. Therefore, patients may experience any chlorpromazine dose-dependent adverse drug reaction.

Interactions in which other drugs are affected by chlorpromazine

Chlorpromazine can increase the depressant action of central nervous system depressants such as benzodiazepines, anaesthetic drugs, opioids, barbiturates and lithium. Chlorpromazine may reduce serum phenytoin levels, may reduce propranolol clearance and may antagonise antidiabetic agents and levodopa, increase valproic acid levels, antagonise the effects of amphetamines, diminish the effect of oral anticoagulants and interact with anticholinergic drugs such as orphenadrine to produce hypoglycaemia.

Cytochrome P450 2D6 Metabolism: Some phenothiazines are moderate inhibitors of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co-administration of chlorpromazine with amitriptyline, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline. Monitor patient for dose-dependent adverse reactions associated with amitriptyline.

Largactil should be avoided in patients taking monamine oxidase inhibitors within the previous 14 days, and monamine oxidase inhibitors should be avoided while using Largactil.

Because of convulsive risk, the combined use of medicinal products which lower the seizure threshold should be carefully assessed.

Gastro-intestinal agents that are not absorbed (magnesium, aluminium and calcium salts, oxides and hydroxides): Reduced gastro-intestinal absorption of phenothiazine neuroleptics may occur. Such gastro-intestinal agents should not be taken at the same time as phenothiazine neuroleptics (at least 2 hours apart, if possible).

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.

Atropine and other atropine derivatives: buildup of atropine-associated adverse effects such as urinary retention, constipation and dry mouth.

Drugs with hypotensive effect: Potentiation of the hypotensive effect and risk of orthostatic hypotension (additive effects).

Guanethidine: Inhibition of the antihypertensive effects of guanethidine.

Chlorpromazine can oppose the effects of adrenaline to produce a paradoxical fall in blood pressure (see Section 4.9 Overdose). It can also oppose the effects of guanethidine and clonidine.

Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Interaction with quinidine may lead to additive myocardial depression. Interaction with MAOIs may lead to additive hypotensive effects. Interactions with suxamethonium, organophosphorus insecticides and atrophine or related drugs are also a possibility.

Chlorpromazine may lower the convulsive threshold; dosage adjustments of anticonvulsants may be necessary (see Section 4.4 Special Warnings and Precautions for Use).

Simultaneous administration of desferrioxamine and prochlorperazine can induce a transient metabolic encephalopathy. Interaction of desferrioxamine and chlorpromazine is a possibility.

Caution is required with the use of the following medicines due to the risk of QT prolongation (see Section 4.4 Special Warnings and Precautions for Use):

- Class Ia antiarrhythmic agents such as quinidine and disopyramide.
- Class III antiarrhythmic agents such as amiodarone and sotalol.
- Other medications such as bepridil, cisapride, sultopride, thioridazine, methadone, intravenous erythromycin, intravenous vincamine, halofantrine, pentamidine, sparflaxacin.
- Medicines which induce bradycardia, such as bradycardia-inducing calcium channel blockers (diltiazem, verapamil), beta-blockers, clonidine, guanfacine, digitalis.
- Medicines which can cause hypokalaemia, such as diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides.
- Other antipsychotics.

4.6 Fertility, pregnancy and lactation

Effects on 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 hyperprolactinemia which can be associated with impaired fertility in women. In men, data on consequences of hyperprolactinemia are insufficient with regard to fertility.

Use in pregnancy – Pregnancy Category D

The use of Largactil is not recommended during pregnancy and in women of childbearing potential not using contraception unless the potential benefits outweigh the potential risks.

Studies in animals by oral route have shown reproductive toxicity (dose related embryo foetotoxicity: increased resorptions and dead foetuses). Increased incidence of malformations was observed in mice but only at doses inducing maternal mortality. There is inadequate animal data regarding reproductive toxicity with chlorpromazine by parenteral route.

Data from available epidemiological studies in children exposed in utero to chlorpromazine cannot exclude the risk of congenital malformations and neurodevelopmental disorders.

Neonates exposed to antipsychotic drugs (including chlorpromazine) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring.

The following effects have also been reported (in postmarketing surveillance) in neonates exposed to phenothiazines during the third trimester of pregnancy:

various degrees of respiratory disorders ranging from tachypnoea to respiratory distress, bradycardia and hypotonia, most often when other drugs such as psychotropic or antimuscarinic drugs were coadministered

signs related to the atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, initial feeding difficulties, abdominal bloating, tachycardia

neurological disorders such as extrapyramidal symptoms including tremor and hypertonia, somnolence, agitation.

Appropriate monitoring and treatment of neonate born to mother receiving chlorpromazine are recommended.

The administered dose and duration of treatment should be as low and short as possible.

Chlorpromazine may occasionally prolong labour and at such a time should be withheld until the cervix is dilated 3 – 4 cm.

Use in lactation

Chlorpromazine has been found to be excreted in breast milk in variable amounts, therefore it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

4.7 Effects on ability to drive and use machines

Patients should be warned about drowsiness, dizziness, and blurred vision and advised not to drive or operate machinery, particularly during the early days of treatment, until they know how Largactil affects them.

4.8 Adverse effects (Undesirable effects)

The following adverse effects have been reported for chlorpromazine or phenothiazines in general.

Nervous System

Very common: sedation or somnolence

Common: parkinsonism

More common: Autonomic: dry mouth, mental confusion, postural hypotension, nasal congestion, nausea, obstipation, constipation, adynamic ileus, urinary retention, priapism, miosis and mydriasis, atonic colon, ejaculatory disorders/impotence.

More common: Central: convulsions, extrapyramidal reactions (parkinsonism, akathisia) tardive dyskinesia, nonextrapyramidal effects including lowering of seizure threshold and paradoxical effects, e.g. agitation, excitement and aggravation of schizophrenic symptoms; drowsiness, dystonias, motor restlessness.

Less common: neuroleptic malignant syndrome (see 4.4 Special Warnings and Precautions for Use)

Less common: Fits, cerebral oedema, nightmares, abnormality of cerebrospinal fluid proteins.

Not known: dizziness, insomnia

Not known: seizure

Not known: dystonia (spasmodic torticollis (not known), oculogyric crises (not known), trismus (not known), etc.)

Not known: tardive dyskinesia, particularly during long term treatment. Tardive dyskinesia may occur after the neuroleptic is withdrawn and resolve after reintroduction of treatment or if the dose is increased.

Extrapyramidal syndrome:

- akinesia (not known) with or without hypertonia (common), partially relieved by anticholinergic antiparkinsonian agents;
- hyperkinetic-hypertonic movements (not known), motor excitation (not known)
- akathisia (very common)

anticholinergic effects such as ileus paralytic (not known), risk of urinary retention (not known), dry mouth (very common), constipation (very common), accommodation disorder (not known)

Local Reactions (injection)

More common: Pain at injection site, injection abscess.

Cardiac disorders

More common: Postural hypotension, 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, atrioventricular block, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest have been reported during neuroleptic phenothiazine therapy, possibly related to dosage.

Less common: Arrhythmias, hypertensive crisis (following abrupt withdrawal), A-V block, ventricular tachycardia, QT interval prolongation and fibrillation.

There have been reports of sudden death, with possible causes of cardiac origin (see Section 4.4 Special Warnings and Precautions for Use), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Not known: torsade de pointes.

Vascular disorders

Not known: orthostatic hypotension, elderly or volume depleted patients are particularly susceptible.

Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs (see Section 4.4 Special Warnings and Precautions for Use).

Respiratory, thoracic and mediastinal disorders

More common: nasal congestion, respiratory depression

Endocrine disorders

More common: Elevated prolactin levels, temperature regulation disorder, hyperglycaemia, other hypothalamic effects.

Less Common: Hyperthermia, hypothermia, lactation and moderate breast engorgement in females on large doses, false-positive pregnancy tests, amenorrhoea, gynecomastia, hypoglycaemia, glycosuria.

Not known: hyperprolactinemia which may result on galactorrhea, erectile dysfunction

Pregnancy, puerperium and perinatal conditions

Not known: drug withdrawal syndrome neonatal

Immune System Disorders

More common: Raised ANA titre, positive SLE cells.

More common: urticaria.

Less common: Allergic reactions.

Very rare: systemic lupus erythematosus. In some cases, positive anti-nuclear antibodies may be seen without evidence of clinical disease.

Not known: hypersensitivity, anaphylactic reaction.

Not known: angioedema.

Renal and urinary disorders

More common: risk of urinary retention

Less common: Inappropriate ADH secretion, water retention, oedema, incontinence.

Blood and lymphatic system disorders

More common: hemolytic anaemia, aplastic anaemia, pancytopenia, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia (including thrombocytopenic purpura).

Less common: Coagulation defects.

Hepatobiliary disorders

Less common: Cholestatic jaundice and liver injury, mainly of hepatocellular, cholestatic or mixed type, sometimes resulting in death, has been reported in patients treated with chlorpromazine (see Section 4.4 Special Warnings and Precautions for Use).

Musculoskeletal

Less common: myasthenia gravis.

Eye Disorders

More common: Blurred vision, photophobia, miosis, mydriasis, corneal deposits (brownish deposits in the anterior segment of the eye caused by accumulation of the drug and generally without effect on vision).

Less common: Precipitation/aggravation of narrow angle glaucoma, optic atrophy, pigmentary retinopathy, lens opacities.

Not known: accommodation disorder.

Psychiatric

Less common: Dysphoria, catatonic excitement.

Not known: confusional state, delirium, anxiety, mood altered.

Serious or Life Threatening Reactions

Of the above the following are potentially life threatening: profound hypotension, cardiac arrhythmia, agranulocytosis, progressive hepatic fibrosis, malignant hyperpyrexia.

Temperature Regulation

Hypothermia or hyperthermia may be life threatening (see Section 4.4 Special Warnings and Precautions for Use). In hot climates, patients are particularly at risk if they are overweight, physically active, and taking high doses of neuroleptics and anti-parkinsonian agents. Physically debilitated, aged, alcoholic and organic brain syndrome patients may also be at risk.

Reproductive system and breast disorders

Very rare: priapism, ejaculation disorder

Investigations

More common: Weight increased.

Not known: abnormal liver function tests

Metabolism and nutrition disorders

Not known: glucose tolerance impaired, hyperglycemia (see 4.4 Special Warnings and Precautions for Use), hypertriglyceridemia, hyponatremia, inappropriate antidiuretic hormone secretion.

Gastrointestinal disorders

Colitis ischemic, intestinal obstruction, gastrointestinal necrosis, necrotizing colitis (sometimes fatal), intestinal perforation (sometimes fatal).

More common: Dry mouth, constipation.

Less common: Paralytic ileus.

Skin and subcutaneous tissue disorders

More Common: Contact dermatitis, photosensitivity reaction, maculopapular, petechial or oedematous reactions.

Less common: Pigmentation disorder and rarely purpura, exfoliative dermatitis and toxic epidermal necrolysis.

Not known: skin reaction, rash.

Other adverse events

In post-marketing surveillance cases of intolerance to glucose and hyperglycaemia have been reported (see Section 4.4 Special Warnings and Precautions for Use).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems (Australia) or <https://nzphvc.otago.ac.nz/reporting/> (New Zealand).

4.9 Overdose

The symptoms of overdosage with chlorpromazine include CNS depression progressing from drowsiness to coma with areflexia; patients with early or mild intoxication may experience restlessness, confusion and excitement. Other symptoms include lethargy, dysarthria, ataxia, stupor, reduction in consciousness into coma, convulsions; mydriasis; cardiovascular symptoms (related to risk of QT interval prolongation), such as hypotension, ventricular tachycardia and arrhythmia; respiratory depression; hypothermia; pupillary constriction; tremor; muscle twitching; spasm or rigidity; convulsions; muscular hypotonia; difficulty in swallowing and breathing; cyanosis and respiratory and/or vasomotor collapse, possibly with sudden apnoea. Polyuria has also been noted which may result in dehydration. Deaths in young children have followed ingestion of 350 to 800 mg of chlorpromazine. Acute toxicity has been determined in animals. LD50 values range from 15 mg/kg (intra-venous, rabbit) to 75 mg/kg (oral, mouse).

These effects may be potentiated by other medicines or by alcohol. Anticholinergic syndrome may occur. Severe parkinsonian syndrome may occur.

In the event of overdose of Largactil, take all appropriate measures immediately.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia) or the National Poisons Information Centre on 0800 POISON or 0800 764 766 (New Zealand).

Treatment

Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by inactivation by administering activated charcoal should be considered. Emetics should not be used, not only

because the antiemetic action of chlorpromazine prevents the effect of the emetic agent, but also because the sedative and extrapyramidal side effects increase the risk of pulmonary aspiration should vomiting occur.

To counter acute hypotension the patient should be placed in the head down position and noradrenaline or phenylephrine administered intravenously. Adrenaline is contraindicated as it may produce a further fall in blood pressure (see Section 4.4 Special Warnings and Precautions for Use).

The central nervous depression should generally be allowed to recover naturally, however, artificial respiration may be required. Appropriate antibiotic therapy should be instituted for any respiratory infections.

Hypothermia should be allowed to recover naturally unless the temperature approaches levels at which cardiac arrhythmias may be feared (e.g. 29.4°C). Shivering is a sign of the waning effects of the drug.

Severe extrapyramidal reactions should be treated with benzotropine or another antiparkinsonian agent (intramuscular dose in adults: 1 to 2mg, children 0.2 to 0.25mg initially with increments if necessary).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Chlorpromazine is a major tranquilliser. It is a phenothiazine, which has antipsychotic actions, the exact basis for which are not fully understood.

Its clinical properties include alleviating anxiety, tension and agitation, potentiating CNS depressants including analgesics, narcotics and sedatives; an antiemetic action.

Chlorpromazine is a dopamine inhibitor. It inhibits prolactin-release-inhibitory factor, considered to be dopamine, thereby stimulating the release of prolactin. The turnover of dopamine in the brain is also increased. The antagonism of central dopaminergic function may be related to the therapeutic effect in psychotic conditions.

Chlorpromazine can produce alpha-adrenergic blockade which may produce hypotension. Chlorpromazine also has a tendency to produce elevated serum glucose and cholesterol levels.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Chlorpromazine is readily absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the gut and the liver. Following oral administration, peak plasma levels are reached in 1 - 4 hours; following intramuscular injection, peak plasma levels usually occur in 15 - 30 minutes. Oral absorption is erratic and incomplete with 10 - 80% of the oral dose reaching the systemic circulation. There is wide inter-subject variation.

Distribution

Chlorpromazine is widely distributed to the body tissue. It crosses the blood-brain barrier and achieves higher concentrations in the brain than in the plasma. The average volume of distribution of chlorpromazine is quite large, ranging from 10 - 35 L/Kg (mean 22 L/Kg). It is highly protein-bound (90 - 99%). Chlorpromazine has been detected in urine for up to one year after discontinuation of chronic administration.

Metabolism

Chlorpromazine metabolism is complex. There is extensive first pass metabolism after oral administration, accounting for a low oral bioavailability of unchanged drug, especially at low oral doses. Over 150 metabolites have been postulated of which about half have been detected in blood and urine. Major metabolic pathways are hepatic and include demethylation, N-oxidation, sulphoxidation, deamination and conjugation. The metabolites of clinical importance appear to be 7- hydroxychlorpromazine, 3- hydroxychlorpromazine, desmethylchlorpromazine and chlorpromazine N-oxide, all of which are biologically active; and chlorpromazine sulphoxide, which is not biologically active. Chlorpromazine is almost completely metabolised with less than 1% excreted in the urine as unchanged drug. Serum levels of unchanged drug and clinical effect do not correlate well. A therapeutic serum level is usually between 100-300ng/mL and toxic effects appear by 750ng/mL but routine serum level monitoring is not necessary. Serum levels in chronic dosing may be lower than those reached after acute dosing.

Excretion

Chlorpromazine and its metabolites are removed from the body significantly in the urine, in small amounts in faeces and in lesser amounts in sweat and hair. Average urinary excretion in 24 hours ranges from 43 - 65% of the daily dose. There is a wide variation in the elimination half lives proposed by various groups, and also wide inter-patient variation. There may be several elimination phases consisting of an early phase of 2 - 3 hours, an intermediate phase of 15 hours and a late phase of up to 60 days.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets

Lactose monohydrate, maize starch, colloidal anhydrous silica, magnesium stearate, hypromellose, macrogol 200. All tablets are coated with opaspray white M-1-7111B (PI 1471).

Syrup

Citric acid, sucrose, caramel, spearmint oil, peppermint oil, essence fruit cup special HC4497 (PI 1747), polysorbate 20, sodium citrate dihydrate, ascorbic acid, sodium sulfite, sodium metabisulfite, sodium benzoate, purified water.

Injection

Sodium sulfite, sodium metabisulfite, sodium chloride, sodium citrate dihydrate, water for injections.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Tablets

Store tablets below 30°C.

Syrup

Store below 25°C. Protect from light.

Injection

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Tablets

25 mg (white, film coated) blister pack: 100s

100 mg (white, film coated) blister pack: 100s

Syrup

100 mL glass type III bottle (25 mg/5 mL)

Glass bottles of 100 mL with PVDC child resistant closure.

Injection

2 mL ampoules (50 mg/2 mL): 10s

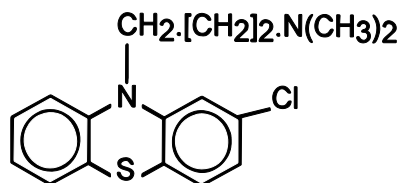
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure

Chemical structure of chlorpromazine hydrochloride:



.HCl

Chlorpromazine is 10-(3-dimethyl-aminopropyl)-2-chlorophenothiazine, a dimethylamine derivative of phenothiazine. Chlorpromazine 100 mg is approximately equivalent to 111 mg of chlorpromazine hydrochloride.

MW = 355.3

Chlorpromazine hydrochloride is an odourless white powder, which decomposes and changes colour on exposure to light. Chlorpromazine hydrochloride is soluble in water, alcohol and chloroform but practically insoluble in ether. The pH of a 10% aqueous solution of the hydrochloride is 4 to 5.

CAS Number

69-09-0

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine (Schedule 4)

8. SPONSOR

Australia

Clinect Pty Ltd
120 – 132 Atlantic Drive
Keysborough VIC 3173
Australia
Free Call Australia: 1800 899 005

New Zealand

Clinect NZ Pty Limited
C/- Ebos Group Limited
108 Wrights Road
Christchurch 8024
New Zealand
Free Call New Zealand: 0800 138 803

9. DATE OF FIRST APPROVAL

21 October 1991

10. DATE OF REVISION

10 October 2023

Summary table of changes

Section Changed	Summary of new information
All	Editorial changes to fonts and styles
All	Removal of 10mg tablet strength
2	List of excipients with known effect: Wording amended to align with declarations printed on the proposed labels
6.5	Addition of detail for child resistant closure bottles.
8.	Updated Sponsor Information