

NEW ZEALAND DATA SHEET

1 LARGACTIL 10 MG, 25 MG, 100 MG FILM COATED TABLETS AND 25 MG/ML SOLUTION FOR INJECTION

Largactil 10 mg film coated tablets

Largactil 25 mg film coated tablets

Largactil 100 mg film coated tablets

Largactil 25 mg/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets: Each tablet contains 10 mg, 25 mg or 100 mg of chlorpromazine hydrochloride

Solution for injection contains 25 mg/mL of chlorpromazine hydrochloride.

Excipients with known effect:

Tablets: Lactose monohydrate

Solution for injection: Sodium metabisulfite and sodium sulfite

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

3 PHARMACEUTICAL FORM

Tablets, Solution for injection

Tablets

10 mg: white to off-white, circular biconvex, film-coated tablets one face impressed LG10 with the reverse side plain film coated tablet

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

Injection

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Chlorpromazine 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 medicines have failed or are not available).
- Childhood schizophrenia and autism.

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of Administration

Oral

Oral administration should be used whenever possible. Dosages should be low to begin with and gradually increase under close supervision until the optimum dosage within the recommended range for the individual is reached. Individuals vary considerably and the optimum dose may be affected by the formulation used. LARGACTIL tablets should not be crushed and solutions should be handled with care because of the risk of contact dermatitis.

The parenteral formulation may be used in emergencies.

Intramuscular

When given by intramuscular route, chlorpromazine must be administered deep into the muscle. As the solution is an irritant, superficial intramuscular administration should be avoided in order to minimize local reactions. LARGACTIL is too irritant to give subcutaneously. Repeated injections should be avoided if possible.

LARGACTIL injection solution has a pH of 5.0 - 6.0 and is incompatible with benzyl-penicillin potassium, pentobarbitone sodium and phenobarbitone sodium. LARGACTIL injection solution, on exposure to light, rapidly develops a pink or yellow colouration; any such solution should be discarded.

Intravenous Infusion

When given by intravenous route, chlorpromazine should be administered as an infusion to minimize local reactions.

Schizophrenia, Psychoses, Anxiety and Agitation

Oral

Adult

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.

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

6 -12 Years: A third to half the adult dose, to a maximum recommended dose of 75 mg daily.

Elderly

Start with a third to a half the usual adult dose with a more gradual increase in dosage.

Intramuscular

Adult

For acute relief of symptoms 25 - 50 mg every 6 – 8 hours.

Children

Under 1 Year: Do not use unless need is life saving.

1-5 Years: 0.5 mg/kg bodyweight every 6 - 8 hours. Dosage is not advised to exceed 40 mg daily.

6-12 Years: 0.5 mg/kg bodyweight every 6 - 8 hours. Not to exceed 75 mg daily.

Elderly

Doses in the lower range for adults should be sufficient to control symptoms, i.e. 25 mg, 8 hourly.

Intractable Hiccup

Oral

Adult

25 - 50 mg three or four times daily.

Children

No information available.

Elderly

No information available.

Intramuscular

Adult

25 - 50 mg every 6-8 hours.

Children

No information available.

Elderly

No information available

Intravenous Infusion

Adult

If other routes of administration are inappropriate, give 25-50 mg in 500-1000 ml sodium chloride by slow intravenous infusion every 6-8 hours.

Children

No information available.

Elderly

No information available.

Nausea and Vomiting of Terminal Illness

Oral

Adults

10 - 25 mg every 4 - 6 hours.

Children

Under 1 Year: Do not use unless need is life saving.

1-5 Years: 0.5 mg/kg every 4 - 6 hours. Maximum daily dosage should not exceed 40 mg.

6 - 12 Years: 0.5 mg/kg every 4 - 6 hours. Maximum daily dosage should not exceed 75 mg.

Elderly

Initially a third to half the adult dose. The physician should then use their clinical judgement to obtain control.

Intramuscular

Adults

25 mg initially, then 25 - 50 mg every 3 - 4 hours until vomiting stops, then drug to be taken orally.

Children

Under 1 Year: Do not use unless need is life saving.

1 - 5 Years: 0.5 mg/kg 6 - 8 hourly. It is advised that maximum daily dosage should not exceed 40 mg.

6-12 Years: 0.5 mg/kg every 6 - 8 hours. It is advised that maximum daily dosage should not exceed 75 mg.

Elderly

For oral use only.

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 (see Section 6.1 List of Excipients).

Bone marrow depression.

Phaeochromocytoma.

Hepatic failure or active hepatic disease.

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 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.

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 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 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 Undesirable Effects).

Photosensitivity

Because of the risk of photosensitization, 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, pheochromocytoma, 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 (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 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 Undesirable Effects).

Hyperglycemia

Hyperglycaemia 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 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 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 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 anti-psychotic 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 anti-psychotic 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.

Use in renal impairment

Chlorpromazine should be given cautiously to patients with renal disease.

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 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

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).

Alcohol use

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

Paediatric use

Children need to be monitored for hypothermia and hypotension.

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 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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 benztropine 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.

Interactions with drugs that may risk QT Prolongation

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, sparfloxacin.
- 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

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.

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 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 mothers receiving chlorpromazine is 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.

Breast-feeding

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 UNDESIRABLE EFFECTS

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

Nervous System

Very common: sedation or somnolence

Not known: dizziness, insomnia

Not known: seizure

Common: parkinsonism

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)

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.

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.

Local Reactions (injection)

More common: Pain at injection site, injection abscess.

Cardiac disorders

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

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.

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

More common: respiratory depression, nasal congestion.

Endocrine disorders

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

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

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

Pregnancy, puerperium and perinatal conditions

Not known: drug withdrawal syndrome neonatal

Immune System Disorders

Not known: hypersensitivity, anaphylactic reaction,

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

More common: Raised ANA titre, positive SLE cells..

More common: urticaria,

Not known: angioedema

Less common: Allergic reactions.

Renal and Urinary Disorders

More common: risk of urinary retention

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

Blood and lymphatic system disorders

Less common: Coagulation defects.

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

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

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

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).

Not known: accommodation disorder.

Psychiatric

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

Less common: Dysphoria, catatonic excitement.

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

Not known: liver function test abnormal

More common: Weight increased

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at <https://nzphvc.otago.ac.nz/reporting/>

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.

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).

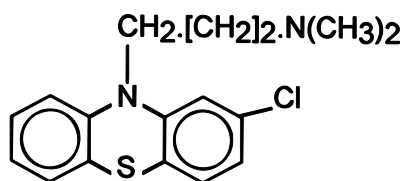
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antipsychotics. ATC code: N05AA01.

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

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

Solution for injection

Sodium chloride

Sodium citrate dihydrate

Sodium metabisulfite

Sodium sulfite

Water for injections

6.2 INCOMPATIBILITIES

Largactil injection solutions have a pH of 5.0-6.5; they are incompatible with benzylpenicillin potassium, pentobarbital sodium and phenobarbital sodium.

6.3 SHELF LIFE

Tablets

36 months.

Solution for injection

60 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Tablets

Store at or below 30°C.

Solution for injection

Stored at or below 25°C.

Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets

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

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

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

Solution for injection

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics

PO Box 62027

Sylvia Park Auckland 1644

Freecall: 0800 283 684

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

31 December 1969

10 DATE OF REVISION OF THE TEXT

20 June 2022

Summary of changes

Section changed	Summary of new information
8	Change of sponsor