

# AUSTRALIAN PRODUCT INFORMATION – LARGACTIL (CHLORPROMAZINE HYDROCHLORIDE)

## 1 NAME OF THE MEDICINE

Chlorpromazine hydrochloride

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets: Each tablet contains 10 mg, 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

Excipients with known effect:

Tablets: Lactose Monohydrate

Syrup: Sucrose, sodium sulfite, sodium metabisulfite, sodium benzoate

Injection: Sodium sulfite, sodium metabisulfite

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

## 3 PHARMACEUTICAL FORM

Tablets, Syrup, Injection Solution

### 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

### 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/or behavioural disturbance in patients with delirium or dementia.

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.

Previous history of a hypersensitivity reaction (e.g. jaundice or blood dyscrasia) to phenothiazines, especially chlorpromazine itself, or to any of the excipients contained in the tablets, syrup or injection.

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.

#### **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.

##### **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.

##### **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 4.4 Adverse Effects (Undesirable Effects)**).

### **Photosensitivity**

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 (sudden death). 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 4.4 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 4.4 Adverse Effects (Undesirable Effects)**).

### **Hyperglycaemia**

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 glycaemic monitoring during treatment (see **Section 4.4 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.

Severe liver toxicity, sometimes resulting in death, has been reported with chlorpromazine use. Patients should be instructed to report immediately signs 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 4.4 Adverse Effects (Undesirable Effects)**).

### **Use in renal impairment**

Chlorpromazine should be given cautiously to patients with renal disease.

### **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***

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.

### **Paediatric use**

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

### **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**

### **Interactions resulting in decreased chlorpromazine levels**

Food, alcohol and benztrapine 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.

Phenothiazines such as chlorpromazine are potent inhibitors of CYP2D6. 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.

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, 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

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

### Use in pregnancy – Pregnancy Category D

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, 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

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

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

#### **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**

Chlorpromazine may impair mental and/or physical abilities, especially during the first few days of therapy. Therefore, caution patients about activities requiring alertness (e.g. operating machinery or vehicles).

#### **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

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

##### **More Common Adverse Effects**

###### ***Cardiovascular***

Postural hypotension, ECG Changes.

###### ***Dermatological***

Contact dermatitis, photosensitivity, urticarial, maculopapular, petechial or oedematous reactions.

###### ***Endocrine***

Elevated prolactin levels, impaired thermoregulation, hyperglycaemia, other hypothalamic effects.

###### ***Gastrointestinal***

Dry mouth, constipation.

###### ***Immunological***

Raised ANA titre, positive SLE cells.

###### ***Genitourinary***

Urinary retention.

###### ***Haematological***

Leucopenia, agranulocytosis, eosinophilia, hemolytic anaemia, aplastic anaemia, thrombocytopenic purpura and pancytopenia have been reported.

### ***Nervous System***

*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.

*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.

### ***Ocular***

Blurred vision, photophobia, miosis, mydriasis, corneal deposits.

### ***Respiratory***

Stuffy nose, respiratory depression.

### ***Local Reactions (injection)***

Pain at injection site, injection abscess.

### ***General***

Weight gain.

## **Less Common Adverse Effects**

### ***Cardiovascular***

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

There have been isolated 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.

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**).

### ***Dermatological***

Skin pigmentation and rarely purpura, exfoliative dermatitis and toxic epidermal necrolysis.

### ***Endocrine***

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

### ***Gastrointestinal***

Paralytic ileus.

### **General**

Rarely, systemic lupus erythematosus has been reported in patients treated with chlorpromazine. In some cases, positive anti-nuclear antibodies may be seen without evidence of clinical disease.

Allergic reactions.

### **Genitourinary**

Inappropriate ADH secretion, water retention, oedema, incontinence.

### **Haematological**

Coagulation defects.

### **Hepatic**

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**

Neuroleptic malignant syndrome, myasthenia gravis.

### **Nervous System**

Fits, cerebral oedema, nightmares, abnormality of cerebrospinal fluid proteins.

### **Ocular**

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

### **Psychiatric**

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.

### **Sudden Death**

Phenothiazine produced sudden death has been reported and is possibly due to cardiac effects (ventricular fibrillation), asphyxia, convulsions or hyperpyrexia. Fortunately, occurrences are rare. There are also reports of unexplained sudden death in patients receiving neuroleptic phenothiazines.

### ***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.

### ***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.

### **Other adverse effects**

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

### ***Metabolism and nutrition disorders***

Hypertriglyceridaemia, hyponatraemia.

### ***Gastrointestinal disorders***

Colitis ischaemic, intestinal obstruction, gastrointestinal necrosis, necrotising colitis (sometimes fatal), intestinal perforation (sometimes fatal).

### ***Skin and subcutaneous tissue disorders***

Angioedema, urticaria.

## 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](http://www.tga.gov.au/reporting-problems).

### 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 hypotension, tachycardia, 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).

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

#### 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, titanium dioxide. 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**

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

#### **Injection**

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

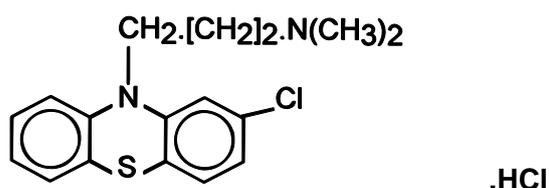
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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:



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

sanofi-aventis australia pty ltd  
12-24 Talavera Road  
Macquarie Park NSW 2113  
Australia

Toll Free Number (medical information): 1800 818 806

Email: [medinfo.australia@sanofi.com](mailto:medinfo.australia@sanofi.com)

## 9 DATE OF FIRST APPROVAL

21 October 1991

## 10 DATE OF REVISION

20 November 2018

### SUMMARY TABLE OF CHANGES

<b>Section Changed</b>	<b>Summary of new information</b>
<b>Overall</b>	Update to formatting in line with current form for providing PI. Editorial changes for improved readability
<b>2</b>	Addition of quantitative formulation with respect to the active ingredient
<b>3</b>	Addition of appearance and appropriate dosage form for each presentation
<b>4.6</b>	Change to pregnancy category from C to D and additional safety warning added.
<b>6.1</b>	Updates to excipients to reflect AAN
<b>6.5</b>	Addition of container type in line with form for providing PI
<b>6.7</b>	Addition of CAS number
<b>8</b>	Addition of contact phone and email