1 PRODUCT NAME

Levomepromazine hydrochloride 25mg/mL injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clear, colourless solution contained in a clear glass ampoule.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.
Clear, colourless solution contained in a clear glass ampoule.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Injection

Levomepromazine hydrochloride is indicated in the management of terminal pain and accompanying restlessness or distress.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage varies with the condition and the individual response of the patient.

Terminal Illness

Injection

Adults

The usual dose for adults is 12.5 - 25 mg (0.5 - 1 mL) by the intramuscular, or after dilution with an equal volume of normal saline, by the intravenous route.

In cases of severe agitation up to 50 mg (2 mL) may be used, repeated every 6 - 8 hours.

Levomepromazine may induce postural hypotension requiring close observation of the patient.

Continuous subcutaneous infusion

Levomepromazine hydrochloride may be administered over a 24 hour period with a syringe driver.

The required dose of levomepromazine hydrochloride (25 - 200 mg per day) should be diluted with the calculated volume of normal saline.

4.3 CONTRAINDICATIONS

- Hypersensitivity to levomepromazine or any of the excipients listed in section 6.1.
- Risk of urinary retention related to urethroprostatic disorders.
- Risk of closed angle glaucoma.
- History of agranulocytosis.
- Dopaminergics, except in patients with Parkinson's disease.

- Safety in pregnancy has not been established. There are no absolute contraindications to the use of levomepromazine in terminal care. The medicine should be avoided or used with caution in patients with liver dysfunction or cardiac disease.
- 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

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

The hypotensive effects of levomepromazine should be taken into account when it is administered to patients with cardiac disease and the elderly or debilitated.

Patients receiving large initial doses should be kept in bed.

Levomepromazine may cause drowsiness, disorientation, confusion or excessive hypotension.

Patients receiving levomepromazine should not drive or operate machinery.

Avoid alcoholic beverages or medicines containing alcohol during treatment.

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.

As with other neuroleptics, very rare cases of QT interval prolongation have been reported.

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

Levomepromazine 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.

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 4.8).

Levomepromazine may lower the epileptic threshold (see Section 4.8**)** and should be used with caution in epileptic patients.

Parkinson's disease. Physicians should weigh the risks versus the benefits when prescribing levomepromazine to patients with Parkinson's disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of neuroleptic malignant syndrome as well as have an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Stroke: In randomised clinical trials of levomepromazine versus placebo performed in a population of elderly patients with dementia and who were treated with certain atypical antipsychotic drugs, a 3-fold increased risk of cerebrovascular events has been observed. The mechanism for this increased risk is not known. An increase in the risk of cerebrovascular events with other antipsychotic drugs or other populations of patients cannot be excluded. levomepromazine should therefore be used with caution in patients with stroke risk factors.

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 levomepromazine 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.

Levomepromazine 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.

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

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, levomepromazine should be used with caution in patients with risk factors for thromboembolism (see Section 4.8).

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: If unexplained fever occurs, treatment should be discontinued since this may be one of the symptoms of the malignant syndrome reported with neuroleptic drugs (pallor, hyperthermia, autonomic disorders, consciousness disorders, muscle rigidity). Signs of autonomic dysfunction, such as sweating and irregular pulse or blood pressure, may precede the onset of hyperthermia and thus constitute early warning signs.

Although this effect of neuroleptics may be idiosyncratic in origin, there may be predisposing risk factors, such as dehydration and organic brain damage.

Apart from exceptional situations, levomepromazine should not be used in patients with Parkinson's disease.

Very rare cases of potentially life-threatening necrotising colitis have been reported (see Section 4.8).

The risk of onset of tardive dyskinesia, even at low doses, particularly in children and the elderly, should be taken into account.

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

Hyperglycaemia or intolerance to glucose has been reported in patients treated with levomepromazine. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of

diabetes who are started on levomepromazine, should get appropriate glycaemic monitoring during treatment (see Section 4.8).

Careful monitoring of treatment with levomepromazine is required in:

- patients with certain cardiovascular diseases, due to the quinidine-like, tachycardia inducing and hypotensive effects of this product class.
- patients with severe hepatic impairment and/or renal impairment, due to the risk of accumulation.

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

Patients should remain lying down for at least one hour after injection due to the risk of hypotension.

During long-term therapy, periodic liver function tests should be performed.

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. Neuroleptic-induced extrapyramidal syndrome should be treated with an anticholinergic agent rather than a dopaminergic.

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 dopaminergics, 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 amfetamine, clonidine, adrenaline.

Levomepromazine will enhance the activity of any sedative or hypnotic.

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.

Simultaneous administration of desferrioxamine and prochlorperazine has been observed to induce a transient metabolic encephalopathy characterised by loss of consciousness for 48-72 hours. It is possible that this may occur with levomepromazin since it shares many of the pharmacological activities of prochlorperazine.

Adrenaline must not be used in patients overdosed with neuroleptics.

Levomepromazine is a moderate inhibitor of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co-administration of levomepromazine with amitriptyline/amitriptylinoxide, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline/amitriptylinoxide. Monitor patients for dose-dependent adverse reactions associated with amitriptyline/amitriptylinoxide.

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

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).

Administration of levomepromazine in patients taking antidiabetic agents can lead to an increase in blood sugar levels. 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.

Medicines that lower blood pressure: Enhanced antihypertensive effect and higher risk of postural hypotension (cumulative effects).

Guanethidine: Inhibition of the antihypertensive effect of guanethidine.

Atropine and atropine-like substances: cumulative adverse effects related to atropine-like substances such as urinary retention, constipation, dry mouth, etc.

Lithium: Risk of developing neuropsychiatric symptoms suggestive of a neuroleptic malignant syndrome or of lithium poisoning.

Interactions with drugs that may risk QT Prolongation

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.

Caution is required with the use of the following medicines due to the risk of QT prolongation (see Section 4.4):

- 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

Use in Pregnancy

Category C

Data from available epidemiological studies in children exposed *in utero* to levomepromazine cannot exclude the risk of congenital malformations. Therefore, the use of levomepromazine is not recommended during pregnancy and in women of childbearing potential not using contraception unless the potential benefits outweigh the potential risks.

No data on the mutagenicity or carcinogenicity of levomepromazine are available.

When tested in the form of the embonate, the material was not teratogenic in the mouse, rabbit or rat.

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 levomepromazine is recommended.

Use in Lactation

Levomepromazine is excreted in breast milk in low amounts. A risk to the breast-fed child cannot be excluded.

Fertility

There are no fertility data in animals.

In humans, levomepromazine interacts with dopamine receptors, which may cause hyperprolactinaemia. This can be associated with impaired fertility in women. Some data suggests that levomepromazine treatment is associated with impaired fertility in men.

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 levomepromazine affects them.

4.8 UNDESIRABLE EFFECTS

Blood and lymphatic system disorders

Agranulocytosis is a rare complication.

Not known: Leukocytopenia, eosinophilia, thrombocytopenia (including thrombocytopenic purpura).

Immune system disorders

Not known: hypersensitivity, urticaria, angioedema

Endocrine disorders

Not known: Thermoregulation disorders, hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea, erectile dysfunction.

Metabolism and nutrition disorders

Not known: Glucose tolerance impaired, hyperglycaemia (see Section 4.4), hyponatraemia (see Section 4.4), ADH inappropriate secretion

Psychiatric Disorders

Not known: Confusional states, delirium, indifference, anxiety, mood altered

Nervous system disorders

Sedation or somnolence and asthenia are frequent, more pronounced at the start of treatment.

Uncommon: Seizures

Not known: Parkinsonism, sedation or somnolence, dizziness, insomnia
Dystonia (spasmodic torticollis, oculogyric crises, trismus, etc.)
Tardive dyskinesia occurring during long-term treatment. Tardive dyskinesia may occur after the neuroleptic agent is withdrawn and resolve after rechallenge or if the dose is

increased. Anticholinergic antiparkinsonian agents have no effect and may cause exacerbation.
Extrapyramidal syndrome:
- akinesia with or without hypertonia, partially relieved by anticholinergic antiparkinsonian agents
- hyperkinetic -hypertonic movements, motor excitation
- akathisia

Neuroleptic malignant syndrome (see Section 4.4)
Anticholinergic effects such as paralytic ileus, risk of urinary retention, dry mouth, constipation, accommodation disorders.

Eye disorders:

Not known: Accommodation disorder, corneal deposits (brownish deposits in the anterior segment of the eye caused by accumulation of the drug and generally without effect on vision).

Cardiac disorders

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

Cases of ventricular arrhythmias, torsades de pointes and cardiac arrest have been reported in post marketing surveillance.

Not known: ECG changes include QT prolongation (as with other neuroleptics), ST depression, U-Wave and T-Wave changes. Cardiac arrhythmias, including ventricular arrhythmias and atrial arrhythmias, a-v block, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest.

Vascular Disorders

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).

Hypotension may occur, especially in elderly patients.

Not known: orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Not known: respiratory depression, nasal congestion

Gastrointestinal Disorders

Necrotizingcolitis, which can be fatal, has been very rarely reported in patients treated with levomepromazine.

Dry mouth is encountered infrequently.

Hepatobiliary disorders

Rare: Jaundice.

Not known: Jaundice cholestatic and liver injury

Skin and subcutaneous tissue disorders

Not known: skin reaction, rash, photosensitivity reaction, pigmentation disorder

Pregnancy, puerperium and perinatal conditions

Not known: Drug withdrawal syndrome neonatal (see Section 4.6)

Reproductive System and Breast Disorders

Not known: Priapism, ejaculation disorder

Investigations

A raised ESR may occasionally be encountered.

Not known: Weight increased, liver function test abnormal, positive serology for antinuclear antibodies without clinical lupus erythematosus.

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 https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

High doses cause depression of the central nervous system, presenting as 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. These effects may be potentiated by other

Severe extra-pyramidal dyskinesis may occur.

If a patient is seen sufficiently soon (up to 6 hours) after ingestion of a toxic dose, gastric lavage may be attempted. Pharmacological induction of emesis is unlikely to be of any use. Activated charcoal should be given. There is no specific antidote. Treatment is supportive.

Generalised vasodilation may result in circulatory collapse; raising the patient's legs may suffice, in severe cases, volume expansion by intravenous fluids may be needed; infusion fluids should be warmed before administration in order not to aggravate hypothermia.

Positive inotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstrictor agents are not generally recommended; avoid the use of adrenaline.

Ventricular or supraventricular tachyarrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life threatening, appropriate anti-arrhythmic therapy may be considered. Avoid lignocaine and, as far as possible, long acting anti-arrhythmic drugs.

Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine or orphenadrine administered either intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam.

Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium may be tried.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antipsychotics, ATC code: NO5AA02

Levomepromazine is a neuroleptic with indications in psychiatry, and in general medicine particularly in terminal illness. Clinically it is more sedative and more potent that chlorpromazine in the management of psychotic conditions and in the relief of chronic severe pain.

Levomepromazine resembles chlorpromazine and promethazine in the pattern of its pharmacology. It possesses analgesic, anti-emetic, anti-histamine and anti-adrenaline activity and exhibits a strong sedative effect. Its precise mechanism of action is unknown.

In studies of the analgesic effect of 15 mg levomepromazine injection, maximum pain relief was achieved 1 hour after intramuscular injection and this had declined by half after a further two hours. A single subcutaneous dose gave good pain relief after 1 hour, which was still effective after 4 hours.

Levomepromazine potentiates the action of other central nervous system depressants but may be given in conjunction with appropriately modified doses of narcotic analgesics in the management of severe pain. levomepromazine does not significantly depress respiration and is particularly useful where pulmonary reserve is low.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

Peak plasma concentrations have been reported 30 to 90 minutes after injection into the gluteal muscle.

Biotransformation

In the urine, up to 5 percent may be excreted unchanged and up to 10 percent as the sulphoxide metabolite. The proportion excreted unchanged via the faeces varied from 0 to 14 percent.

Elimination

Excretion is slow with a half-life of about 30 hours and is via the urine and faeces.

5.3 PRECLINICAL SAFETY DATA

No further relevant information other than that which is included in the other sections of the Data Sheet

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The injection also contains:
Ascorbic acid
Sodium sulfite
Sodium chloride
Water for injections.

6.2 INCOMPATIBILITIES

Levomepromazine hydrochloride injection solution is incompatible with alkaline solutions.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light. Levomepromazine hydrochloride injection solution, on exposure to light, rapidly develops a pink or yellow colouration and any such solution should be discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

1ml neutral glass (Type 1) ampoule. Each pack contains 10 ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Dilution of levomepromazine injection in normal saline is compatible with diamorphine hydrochloride, which may be added if greater analgesia is required.

Dilutions of levomepromazine injection in normal saline, with or without the addition of diamorphine hydrochloride are stable for 24 hours.

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Max Health Ltd
PO Box 44452
Pt Chevalier, Auckland 1246
Telephone: (09) 815 2664.

UK Marketing Authorisation Holder:
Wockhardt UK Ltd
Ash Road North
Wrexham, LL13 9UF, UK

9 DATE OF FIRST APPROVAL

07 April 2016

10 DATE OF REVISION OF THE TEXT

5 April 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3	Addition of children younger than 1 year
4.4	Additional warnings included
4.5	Additional interactions included
4.7	Information expaanded
4.8	Additional undesirable effects included
4.9	Information expanded.