1 PRODUCT NAME

Levomepromazine hydrochloride 25mg/mL injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the solution contains Levomepromazine hydrochloride 25mg.

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

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 - 25mg (0.5 - 1ml) by the intramuscular, or after dilution with an equal volume of normal saline, by the intravenous route.

In cases of severe agitation up to 50mg (2ml) 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 - 200mg per day) should be diluted with the calculated volume of normal saline.

Elderly

No specific dosage recommendations.

4.3 Contraindications

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

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 hydrochloride 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 hydrochloride may cause drowsiness, disorientation, confusion or excessive hypotension. Patients receiving levomepromazine hydrochloride should not drive or operate machinery.

Avoid alcohol.

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

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 4.8 Undesirable effects).

Levomepromazine hydrochloride may lower the epileptic threshold (see 4.8 Undesirable effects) and should be used with caution in epileptic patients.

Parkinson's disease. Physicians should weigh the risks versus the benefits when prescribing levomepromazine hydrochloride 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 and postural instability with frequent falls, in addition to extrapyramidal symptoms.

A 3-fold increased risk of cerebrovascular events has been reported in elderly patients with dementia treated with atypical antipsychotic medicines. An increase in the risk of cerebrovascular events with other antipsychotic medicines or other populations of patients cannot be excluded. Levomepromazine hydrochloride should therefore be used with caution in patients with stroke risk factors.

Elderly patients with dementia-related psychosis treated with antipsychotic medicines 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 medicines, treatment with conventional antipsychotic medicines may increase mortality. The extent to which the findings of increased mortality in observational studies may be

attributed to the antipsychotic medicine as opposed to some characteristic(s) of the patients is not clear.

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

Hyperglycaemia or intolerance to glucose has been reported in patients treated with levomepromazine hydrochloride. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on levomepromazine hydrochloride, should get appropriate glycaemic monitoring during treatment (see 4.8 Undesirable effects).

4.5 Interaction with other medicines and other forms of interaction

Levomepromazine will enhance the activity of any sedative or hypnotic.

Avoid 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 levomepromazine hydrochloride since it shares many of the pharmacological activities of prochlorperazine.

Adrenaline must not be used in patients overdosed with neuroleptics.

Coadministration of levomepromazine and medicines primarily metabolised by the cytochrome CYP2D6 enzyme system may result in increased plasma concentrations of these medicines.

Monitor patients for dose-dependent adverse reactions associated with CYP2D6 substrates such as amitriptyline.

Interactions with medicines that may risk QT Prolongation

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

<u>Pregnancy</u>

Category C.

Levomepromazine hydrochloride is not recommended during pregnancy.

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 medicines such as psychotropic or antimuscarinic medicines 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 hydrochloride is recommended.

Breast-feeding
Levomepromazine is excreted in breast milk in low amounts in human milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Levomepromazine Injection therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no fertility data in animals.

In humans because of the interaction with dopamine receptors, levomepromazine may cause hyperprolactinaemia which can be associated with impaired fertility in women. Some data suggest that levomepromazine treatment is associated with impaired fertility in men.

4.7 Effects on ability to drive and use machines
Patients receiving levomepromazine hydrochloride should not drive or operate machinery.

4.8 Undesirable effects
Somnolence and asthenia are frequent, but subside as treatment progresses.

Dry mouth is encountered infrequently.

Hypotension may occur, especially in elderly patients.

A raised ESR may occasionally be encountered.

Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported.

Agranulocytosis is a rare complication.

Photosensitivity and allergic skin reactions have occasionally been reported.

Parkinsonism-like reactions sometimes occur, but they are seldom noted except in patients receiving prolonged high dosage.

Confusional states, delirium and convulsions have been reported.

Jaundice is a rare side-effect.

Hepatocellular, cholestatic and mixed liver injury have been reported.

Other adverse effects common to phenothiazine neuroleptics may be seen, such as QT interval prolongation.

There have been isolated reports of sudden death, with possible causes of cardiac origin (see 4.4 Special warnings and precautions for use.

Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic medicines (see 4.4 Special warnings and precautions for use).

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

Priapism has also been very rarely reported.

Hyperglycaemia or intolerance to glucose has been reported with antipsychotic phenothiazines (see 4.4 Special warnings and precautions for use).

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

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms of levomepromazine overdosage include:

- drowsiness or loss of consciousness, convulsions, hypotension, tachycardia, ECG changes, ventricular arrhythmias and hypothermia. Severe extra-pyramidal dyskinesis may occur.

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 medicines.

Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine (5-10mg) or orphenadrine (20 - 40mg) 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

ATC Code: NO5AA02
Pharmacotherapeutic group: Antipsychotics.

Levomepromazine hydrochloride 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 15mg levomepromazine hydrochloride 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 hydrochloride 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 hydrochloride 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

There are no pre-clinical safety data of relevance to the prescriber which are additional to those already included in other sections of the datasheet.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The injection also contains the following excipients per mL:

Ascorbic acid 1 mg/mL
Sodium sulphite 0.5 mg/mL
Sodium chloride 7.50 mg/mL
Water for injection q.s.

6.2 Incompatibilities

Levomepromazine hydrochloride injection solution is incompatible with alkaline solutions.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or 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.

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

Dilutions of Levomepromazine hydrochloride injection in normal saline, with or without the addition of diamorphine hydrochloride are stable for 24 hours. However, the lack of preservative means that the product should be used in a closed system.

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

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 65 231
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Auckland 0754

Telephone: (09) 815 2664.

UK Marketing Authorisation Holder:
Wockhardt UK Ltd
Ash Road North
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9 DATE OF FIRST APPROVAL

07 April 2016

10 DATE OF REVISION OF THE TEXT

03 October 2018

SUMMARY TABLE OF CHANGES

Date of Revision	Section Changed	Summary of new information
03 October 2018	All	• Updated to new SPC format and current reference product datasheet.