NAME OF THE MEDICINE

Levomepromazine hydrochloride 25mg/mL injection.

PRESENTATION

Injection
Colourless isotonic injection solution 25 mg per mL levomepromazine hydrochloride in ampoules of 1 mL.

USES

Actions

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 than 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.

Pharmacokinetics

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.

INDICATIONS

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

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.

**PRECAUTIONS**

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 **ADVERSE EFFECTS**).

Levomepromazine hydrochloride may lower the epileptic threshold (see **ADVERSE 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 **ADVERSE 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 ADVERSE EFFECTS).

Use in Pregnancy
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.

Effects on Ability to Drive and Use Machines

Patients receiving levomepromazine hydrochloride should not drive or operate machinery.

ADVERSE 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 PRECAUTIONS), 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 medicines (see PRECAUTIONS).
Levomepromazine hydrochloride

Levomepromazine hydrochloride 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 PRECAUTIONS).

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

INTERACTIONS

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 P450 2D6 enzyme system may result in increased plasma concentrations of these medicines.

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 PRECAUTIONS):

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

DOSAGE AND 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.

OVERDOSAGE

Symptoms of levomepromazine overdose include:
drowsiness or loss of consciousness, convulsions, hypotension, tachycardia, ECG changes, ventricular arrhythmias and hypothermia. Severe extra-pyramidal dyskinesia 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.

PRESENTATION AND STORAGE CONDITIONS

Injection solution 25mg/mL, box of 10 x 1mL ampoules.
Store at or below 25°C.

Special Precautions for Storage
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.

Incompatibilities
Levomepromazine hydrochloride injection solution is incompatible with alkaline solutions.

FURTHER INFORMATION

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.
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.

MEDICINES CLASSIFICATION
Prescription Medicine.

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