

DATASHEET

NOZINAN[®]

NAME OF THE MEDICINE

Levomepromazine hydrochloride 25mg/mL injection. Levomepromazine maleate 25mg and 100mg tablets.

PRESENTATION

Injection

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

Tablets

White, biconvex film-coated tablets containing 25 mg and 100 mg levomepromazine maleate indented 'L25' and 'L100' respectively on one face with a break-line on the reverse. The diameter of the 25 mg tablets is 8.7 mm and the 100 mg tablets 11.0 mm.

USES

Actions

Nozinan 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 15 mg Nozinan 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.

Nozinan 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. Nozinan does not significantly depress respiration and is particularly useful where pulmonary reserve is low.

Pharmacokinetics

Absorption

With the oral presentations, maximum serum concentrations are achieved in 1-3 hours.

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

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

Tablets

Psychiatry

As an alternative to Largactil in schizophrenia, especially when it is desirable to reduce psychomotor activity.

General Medicine

Alone or together with appropriately modified doses of analgesics and narcotics, in the relief of severe pain and accompanying anxiety and 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 Nozinan 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 Nozinan 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.

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

Patients receiving Nozinan 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, 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 **ADVERSE EFFECTS**).

Nozinan 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 Nozinan 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.

A 3-fold 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. Nozinan should therefore be used with caution in patients with stroke risk factors.

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.

Cases of venous thromboembolism, sometimes fatal, have been reported with antipsychotic drugs. Therefore, Nozinan 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 Nozinan. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on Nozinan, should get appropriate glycaemic monitoring during treatment (see **ADVERSE EFFECTS**).

Use in Pregnancy

Category C

Nozinan 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 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 Nozinan is recommended.

Effects on Ability to Drive and Use Machines

Patients receiving Nozinan 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 patient 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 drugs (see **PRECAUTIONS**).

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 have 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 Nozinan since it shares many of the pharmacological activities of prochlorperazine.

Adrenaline must not be used in patients overdosed with neuroleptics.

Coadministration of levomepromazine and drugs primarily metabolised by the cytochrome P450 2D6 enzyme system may result in increased plasma concentrations of these drugs.

Interactions with drugs that may risk QT Prolongation

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

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 - 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

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

Nozinan DS

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

Tablets

Nozinan tablets 25 mg may be substituted for the injection if oral therapy is more convenient.

The dosage is 12.5 - 50 mg every 4 - 8 hours.

Elderly

No specific dosage recommendations.

Psychiatry

Tablets

Adults

Ambulant patients:

Initially the total daily dose should not exceed 25 - 50 mg, usually divided into three doses.

A larger portion of the dosage may be taken at bedtime to minimise diurnal sedation.

The dosage is then gradually increased to the most effective level coupled with minimum side-effects.

Bed patients:

Initially the total dosage may be 100 mg to 200 mg, usually divided into three doses, gradually increased to 1 g daily if necessary.

Attempts should be made when the patient is stable to reduce the dosage to an adequate maintenance level.

Children

Children are very susceptible to the hypotensive and soporific effects of levomepromazine. It is advised that a total daily oral dose of 40 mg should not be exceeded.

The average effective daily intake for a 10 year old is 15 mg - 20 mg in divided doses.

Elderly

It is not advised to give levomepromazine to ambulant patients over 50 years of age unless the risk of a hypotensive reaction has been assessed.

OVERDOSAGE

Symptoms of levomepromazine overdosage include:

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

(5-10 mg) or orphenadrine (20 - 40 mg) 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 25 mg/mL, box of 10 x 1 ml ampoules

Containers of 100 x 25 mg and 100 x 100 mg tablets

Special Precautions for Storage

Protect from light. Nozinan injection solution, on exposure to light, rapidly develops a pink or yellow colouration and any such solution should be discarded.

Incompatibilities

Nozinan injection solution is incompatible with alkaline solutions.

FURTHER INFORMATION

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

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

Nozinan 25 mg tablets contain magnesium stearate, calcium hydrogen phosphate, potato starch and sodium lauryl sulphate.

Nozinan 100 mg tablets contain stearic acid, potato starch, calcium carbonate and sodium lauryl sulphate.

The injection also contains ascorbic acid, sodium sulphite and sodium chloride.

MEDICINES CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF SPONSOR

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