

DATA SHEET

1 NOZINAN (SWISS STOCK)

Nozinan (Swiss stock) 25 mg and 100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levomepromazine 25mg equivalent to 33.75 mg levomepromazine maleate

Levomepromazine 100mg equivalent to 135 mg levomepromazine maleate.

Excipient with known effect: lactose monohydrate. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Beige, biconvex film-coated tablets indented ' NN 25' and 'NN 100 ' respectively on one face with a break-line on the reverse. The diameter of the 25 mg tablets is 9 mm and the 100 mg tablets 12 mm.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

The below recommended doses refer to the amount of levomepromazine maleate contained in the Nozinan tablets.

Terminal Illness

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.

4.3 CONTRAINDICATIONS

Hypersensitivity to levomepromazine or any of the excipients listed in section 6.1 or any other phenothiazines and thioxanthenes.

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 Nozinan 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 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 alcoholic beverages or medicines containing alcohol during treatment.

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 Section 4.8).

Nozinan 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 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.

Stroke: In randomised clinical trials of Nozinan 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. Nozinan should therefore be used with caution in patients with stroke risk factors.

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.

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 Section 4.8).

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, Nozinan should not be used in patients with Parkinson's disease.

The onset of paralytic ileus, which may be manifested by distension and abdominal pain, should be treated as an emergency.

Very rare cases of potentially fatal necrotising enterocolitis have been reported (see Section 4.8).

Nozinan should be avoided in hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis, prostate hypertrophy.

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

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 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.
- elderly patients exhibiting greater susceptibility to orthostatic hypotension, sedation and extrapyramidal effects; chronic constipation (risk of paralytic ileus); possible prostatic hypertrophy.

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

Dopaminergics in patients with Parkinson's disease. Mutual antagonism between dopaminergics and neuroleptics. 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”).

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.

Combinations requiring precaution

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 CYP2D6 enzyme system may result in increased plasma concentrations of these drugs. Monitor patients for dose-dependent adverse reactions associated with CYP2D6 substrates such as amitriptyline/amitriptylinoxide.

The combined use of medicinal products that are proconvulsant, or lower the seizure threshold, should be carefully weighed up due to the severity of the incurred risk (see Section 4.4).

Combinations to be taken into consideration

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

Guanethidine: Inhibition of the antihypertensive effect of guanethidine (inhibition of guanethidine uptake into sympathetic fibre, its site of action).

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 Nozinan cannot exclude the risk of congenital malformations. Therefore, the use of Nozinan 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 Nozinan 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 receiving Nozinan should not drive or operate machinery.

4.8 UNDESIRABLE EFFECTS

Blood and lymphatic system disorders

Agranulocytosis is a rare complication, regular complete blood count is recommended.

Not known: Leukocytopenia.

Endocrine disorders

Not known: Thermoregulation disorders, hyperprolactinaemia which may result in galactorrhoea, gynaecomastia, amenorrhoea, impotence, frigidity.

Metabolism and nutrition disorders

Not known: Intolerance to glucose, hyperglycaemia (see Section 4.4), hyponatraemia (see Section 4.4), ADH inappropriate secretion

Psychiatric Disorders

Not known: Confusional states, delirium, indifference, anxiety reactions, mood changes

Nervous system disorders

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

Uncommon: Convulsions

Not known: Parkinsonism (with prolonged high dosage),
Early dyskinesia (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: Brownish deposits in the anterior segment of the eye caused by accumulation of the drug and generally without effect on vision.

Cardiac disorders

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: Postural hypotension

Gastrointestinal Disorders

Necrotizing enterocolitis, 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: Hepatocellular, cholestatic and mixed liver injury have been reported.

Skin and subcutaneous tissue disorders

Photosensitivity and allergic skin reactions have occasionally been reported.

Pregnancy, puerperium and perinatal conditions

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

Reproductive System and Breast Disorders

Priapism has also been very rarely reported.

General disorders and administration site conditions

There have been isolated 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.

Investigations

A raised ESR may occasionally be encountered.

Not known: Weight gain, 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://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 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 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

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.

5.2 PHARMACOKINETIC PROPERTIES

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.

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

Nozinan 25 mg tablets contain lactose monohydrate, wheat starch, hydrated colloidal silica; dextrin, magnesium stearate, hypromellose; macrogol, titanium oxide, yellow iron oxide E172.

Nozinan 100 mg tablets contain lactose monohydrate, wheat starch, hydrated colloidal silica; dextrin; magnesium stearate, hypromellose; macrogol, titanium oxide, yellow iron oxide E172
Incompatibilities

Not applicable

6.2 SHELF LIFE

Blister pack 100mg 36 months from date of manufacture

Blister pack 25mg 36 months from date of manufacture

6.3 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.4 NATURE AND CONTENTS OF CONTAINER

Blisters of 100 x 25 mg and 100 x 100 mg tablets

6.5 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

sanofi aventis new zealand limited

Level 8, 56 Cawley Street, Ellerslie,

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9 DATE OF FIRST APPROVAL

31 December 1969

10 DATE OF REVISION OF THE TEXT

12 February 2020