Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nozinan 25 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml ampoule contains 25mg of Levomepromazine Hydrochloride.
Each 1ml also contains 0.5mg sodium sulphite and total sodium 2.7 mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear, bright pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of schizophrenia and other major psychoses including mania and hypomania.
As an adjunct in the relief of severe terminal pain with accompanying anxiety, restlessness or distress.

4.2 Posology and method of administration

Route of administration:
Intramuscular, Intravenous or Continuous subcutaneous Use.

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

Adults:
The usual daily dosage is 12.5 - 25 mg (0.5-1 ml) by intramuscular injection or by the intravenous route after dilution with an equal volume of normal saline immediately before use. In cases of severe agitation, up to 50 mg (2 ml) may be used, repeated every 6 to 8 hours.

Continuous subcutaneous infusion:
Nozinan may be administered over a 24-hour period via a syringe driver. The required dose of Nozinan (25-200 mg per day) should be diluted with the calculated volume of normal saline. Diamorphine hydrochloride is compatible with this solution and may be added if greater analgesia is required.

Elderly:
No specific dosage recommendations.

4.3 Contraindications

- Hypersensitivity to levompromazine or any of the other ingredients (see Section 6.1).
- In combination with:
    - citalopram, escitalopram,
    - hydroxyzine
    - piperaquine
    - domperidone.

4.4 Special warnings and precautions for use

In case of a persistent fever, sore throat or infection under levomepromazine use a complete blood count is advised. Treatment should be stopped in the case of leucytosis, or leucopenia.

Neuroleptic malignant syndrome:
Nozinan has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia), altered consciousness and increased serum creatine phosphokinase levels. Hyperthermia is often an early sign of this syndrome. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Antipsychotic treatment must be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Phenothiazines should only be used with great caution in patients with a history of jaundice or with existent liver dysfunction or blood dyscrasias.

Patients receiving phenothiazines over a prolonged period require regular and careful surveillance with particular attention to potential for inducing eye changes, effects on haemopoiesis, liver dysfunction, myocardial conduction effects, particularly if other concurrently administered drugs also have potential effects on these systems.

Use of phenothiazines at high (relative or absolute) doses may induce extrapyramidal side effects, dyskinesia, akathisia, dystonia. These are likely to be particularly severe in children.

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

In common with other anti-psychotics levomepromazine has been associated with persistent dyskinesia. Tardive dyskinesia may develop in some patients on long term therapy, possibly in relation to total cumulative dose, or may develop after drug therapy has been discontinued. The risk is reported to be greater in elderly patients on high-dose therapy.

Characteristic symptoms are rhythmical involuntary movements of the tongue, face, mouth or jaw sometimes accompanied by involuntary movements of the extremities. They may persist for many months or even years and, while they gradually disappear in some patients, they appear to be permanent in others.

At first signs of tardive dyskinesia which may be orofacial dyskinesia the benefit of continued treatment should be carefully assessed against the risk of the development of persistent dyskinesia. Withdrawal of treatment with careful observation of the dyskinesia and psychotic condition has been suggested in order to assess the need for continued neuroleptic therapy and to reveal persisting dyskinesia. Should it be necessary to reinstate treatment, the anti-psychotic agent may mask the syndrome. Anti-parkinsonian agents have proved of little value in this syndrome.

Phenothiazines should be used with particular care in the presence of extremes of temperature because of its capacity to interfere with the body's thermoregulation.
Phenothiazines should only be used with great caution in patients with coronary insufficiency or cardiovascular disorders which may predispose to prolongation of the QT interval.

Prolonged QT Interval:
Levomepromazine hydrochloride prolongs the QT interval dose-dependently. This effect, which is known to potentiate the risk of onset of serious ventricular arrhythmias of the torsades de pointes type, which is potentially fatal (sudden death), is exacerbated in the presence of bradycardia, hypokalaemia, and congenital or acquired QT prolongation (combination with a drug inducing QT interval prolongation) (see Section 4.8). It is therefore important to ensure the absence of factors which may promote the onset of this rhythm disorder prior to administration, if the clinical situation allows:
- Bradycardia of less than 55 beats per minute
- Electrolyte imbalance in particular hypokalaemia
- Congenital QT interval prolongation
- Ongoing treatment with a medicinal product liable to induce significant bradycardia (<55 beats per minute), hypokalaemia, delayed intracardiac conduction or QT interval prolongation (see Sections 4.3 and 4.5).

Except in emergencies, it is recommended that an ECG be performed as part of the initial evaluation of patients due to receive treatment with a neuroleptic agent.

Except in special cases, this drug should not be administered to patients with Parkinson's disease.

Levomepromazine may cause abdominal pain and distention mimicking of paralytic ileus which should be treated as an emergency.

Avoid concomitant prescription of other antipsychotics.

The hypotensive effects of Nozinan should be taken into account when administered to patients with cardiac disease and the elderly or debilitated. Patients receiving large initial doses should be kept in bed. Phenothiazine treated patients who experience postural hypotension should be cautioned to not get up quickly and to obtain assistance when necessary.

Levomepromazine should be used with caution in hypothyroidism, cardiac failure, phaeochromocytoma, myasthenia gravis, prostate hypertrophy.

Monitoring of treatment with levomepromazine must be intensified in the following cases:

- Epileptic patients, as levomepromazine may lower the seizure threshold (see Section 4.8) and should be used with caution in epileptic patients. Treatment must be discontinued if seizures occur.
- Elderly patients with: greater susceptibility to postural hypotension, sedation and extrapyramidal effects, chronic constipation (risk of paralytic ileus), possible prostatic hypertrophy
- Patients with certain cardiovascular diseases, due to the quinidine-like, tachycardia-inducing and hypotensive effects of this product class.
- Patients with severe hepatic and/or renal insufficiency, due to the risk of accumulation.
- In patients with agranulocytosis, regular blood count is recommended (see Section 4.8)
- Especially during prolonged treatments, tardive dyskinesia sometimes occurs upon discontinuation of the neuroleptic and disappears when it is reintroduced or the dosage is increased.

Patients are strongly advised not to consume alcohol or to take medicines containing alcohol during treatment (see Section 4.5).

Excipient(s) with known effect
Sulphites: This medicinal product contains "sulphites" and can cause severe allergic reactions and bronchospasm.

Sodium: This medicinal product contains less than 1mmol sodium (23 mg) per ml, that is to say essentially 'sodium free'.

Stroke:
In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patients cannot be excluded. Nozinan should 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 cause 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.

Venous Thromboembolism:
Cases of venous thromboembolism (VTE) have been reported with antipsychotics. As patients treated with antipsychotics often have acquired risk factors for VTE, any potential risk factor for VTE should be identified before and during treatment with Nozinan and preventive measures must be implemented (see Section 4.8).

Hyperglycaemia:
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).

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations (see Section 4.3):

Citalopram, escitalopram, hydroxyzine, piperaquine, domperidone: increased risk of ventricular arrhythmias, particularly torsades de pointes.

Combinations not recommended (see section 4.4):

Levodopa: mutual antagonism between levodopa and neuroleptics. In patients with Parkinson's disease, minimum effective doses of each of these drugs should be used.

Dopaminergics (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole): 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 dopaminergic agonists, the latter should be tapered off gradually (sudden discontinuation of dopaminergic agents exposes the patient to a risk of 'neuroleptic malignant syndrome').

Drugs that may induce torsades de pointes: class Ia anti-arrhythmics (quinidine, hydroquinidine, disopyramide); class III anti-arrhythmics (amiodarone, dofetilide, ibutilide, sotalol); certain neuroleptics: phenothiazines (chlorpromazine, cyamemazine, thioridazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); and others such as: bepridil, cisapride, diphenmanil, erythromycin IV, mizolastine, vincamine IV.

Other medications that may cause torsades de pointes (halofantrine, moxifloxacin, pentamidine, sparfloxacin): increased risk of ventricular arrhythmias, particularly torsades de pointes. If possible, discontinue the non-anti-infective torsadogenic drug. If co-administration cannot be avoided, prior monitoring of the QT interval and ECG should be performed.

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.

Combinations which should be used with precaution:

Topical agents for gastro-intestinal use (magnesium, aluminium and calcium salts, oxides and hydroxides): decreased gastro-intestinal absorption of phenothiazine neuroleptics. Allow for an interval between administration of topical gastrointestinal agents and phenophiazine neuroleptic agents (more than 2 hours apart, if possible).

Bradycardia-inducing medications (bradycardia-inducing calcium antagonists: diltiazem, verapamil; beta-blockers (except sotalol); clonidine: guanfacine; digitalis products): increased risk of ventricular arrhythmias, particularly torsades de pointes. Vasodilator effect and risk of hypotension, particularly in orthostatic hypotension (additive effect). Clinical and electrocardiographic monitoring.

Potassium lowering drugs (potassium-lowering diuretics, stimulant laxatives, amphotericin B (IV route), glucocorticoids, tetracosactide): increased risk of ventricular arrhythmias, particularly torsades de pointes. Hypokalaemia should be corrected before administering the medicinal product. Clinical, electrolyte and electrocardiographic monitoring.

Cytochrome P450 2D6 Metabolism: Levomepromazine and its non-hydroxylated metabolites are reported to be inhibitors of cytochrome P450 2D6 (CYP2D6). There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co-administration of levomepromazine and drugs primarily metabolized 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.

Other medicinal products which lower the seizure threshold: increased risk of seizures.

Combinations to be taken into consideration:

Antihypertensive agents: enhanced antihypertensive effect and higher risk of postural hypotension (cumulative effects). For guanethidine, see below.

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

Orlistat: Risk of therapeutic failure in the case of concomitant treatment with orlistat.

Atropine and atropine-like substances: imipramine antidepressants, anticholinergic H^1-antihistamines, anticholinergic antiparkinsonian agents, atropine-like antispasmodics, disopyramide): cumulative adverse effects related to atropine-like substances such as urinary retention, constipation, dry mouth, etc.

Dapoxetine: Risk of increased undesirable effects, particularly vertigo and syncope.

Other central nervous system depressants: morphine derivatives (analgesics, antitussives and replacement therapies); barbiturates; benzodiazepines; non-benzodiazepine anxiolytics (carbamates, captodiam, etifoxine); hypnotics; sedative antidepressants; sedative H^1-antihistamines; centrally acting antihypertensive agents; baclofen; thalidomide: enhanced central nervous system depression. Impaired alertness may be hazardous for driving and operating machines.

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

Alcohol (beverage or excipient): Alcohol increases the sedative effect of these substances. Respiratory depression may occur. Decreased alertness may make driving vehicles and using machines dangerous. Avoid the consumption of alcoholic beverages and other medicinal products containing alcohol.

The injection is incompatible with alkaline solutions. Diamorphine hydrochloride is compatible with the solution if required.

4.6 Fertility, pregnancy and lactation

Pregnancy
The clinical data with levomepromazine are reassuring but still limited, and animal studies are insufficient for a conclusion to be reached regarding reproductive toxicity. In humans, the teratogenic risk of levomepromazine has not been evaluated. Different prospective epidemiological studies conducted with other phenothiazines have yielded contradictory results regarding teratogenic risk.

Neonates exposed to antipsychotics (including Nozinan) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, bradycardia, tachycardia, feeding disorder, meconium ileus, delayed meconium passage, abdominal bloating.

Given these data, it is preferable to avoid using Nozinan during pregnancy as a precautionary measure and neonates must be closely monitored in the event of treatment at the end of pregnancy.

The injectable neuroleptics used in emergency situations can trigger maternal hypotension.

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

Breast-feeding is not recommended during treatment.

Fertility
There are no data on fertility 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

Phenothiazines may induce drowsiness, disorientation and confusion. Persons taking these drugs should not drive or operate machinery unless the drug has been shown not to interfere with physical or mental ability.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common ≥ 10%; Common ≥ 1 to < 10%; Uncommon ≥ 0.1 to < 1%;
Rare ≥ 0.01 to < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

General Disorders and Administration Site Conditions:
There have been isolated reports of sudden death with possible causes of cardiac origin (see also Section 4.4), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Metabolism and Nutrition Disorders:
*Not known:*Hyponatraemia (see Section 4.4), Syndrome of Inappropriate Antidiuretic Secretion (SIADH)

Psychiatric Disorders:
Not known: Confusional states, delirium

Nervous System Disorders:
Not known: Confusional states, convulsions. Neuroleptic malignant syndrome (see Section 4.4).

Vascular Disorders:
Cases of venous thromboembolism*(uncommon)*, including cases of pulmonary embolism *(not known)* sometimes fatal, and cases of deep vein thrombosis*(not known)* have been reported with antipsychotic drugs (see also Section 4.4). Postural hypotension.

Gastrointestinal Disorders:
Not known: Necrotizing enterocolitis, which can be fatal, has been reported in patients treated with levomepromazine.

Hepatobiliary Disorders:
Not known: Hepatocellular, cholestatic and mixed liver injury

Reproductive System and Breast Disorders
Very rare: Priapism

Starting at low doses:

Autonomic Disturbances:

- Anticholinergic effects such as dry mouth, accommodation disorders, risk of urinary retention, constipation and even paralytic ileus.

Neuropsychiatric Disorders:

- Sedation or somnolence, particularly at the start of treatment.
- Anxiety reactions, mood changes.

At higher doses:
Neuropsychiatric Disorders:

- Parkinsonism (with prolonged high dosage)
- Early-onset dyskinesa (spasmodic torticollis, oculogyric crises, trismus, etc).
- Extrapyramidal syndrome:
    - akinetic symptoms with or without hypertonia, partially relieved by anticholinergic antiparkinsonian agents
    - hyperkinetic-hypertonic movements with excitatory motor behavioural activity
- Tardive dyskinesia
- Anticholinergic antiparkinsonian agents have no effect and may cause exacerbation.

Endocrine and Metabolic Disorders:

- Hyperprolactinemia: amenorrhea, galactorrhea, gynecomastia, impotence.
- Alteration in temperature regulation.
- Hyperglycemia, diabetes, impaired glucose tolerance (see Section 4.4).

Rare and dose-dependent:

Cardiac Disorders:

- ECG changes include QT interval 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 have been reported during neuroleptic phenothiazine therapy, possibly related to dosage.
- Very rare cases of torsades de pointes have been reported.

Non-dose-dependent and more rarely reported:

Skin and Subcutaneous Disorders:

- Allergic skin reactions
- Photosensitisation.

Blood and Lymphatic System Disorders:

- Leukopenia.
- Not known: agranulocytosis
- Treatment should be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the blood count.
- Not known: thrombocytopenia (including thrombocytopenic purpura), eosinophilia

Eye Disorders:

- Brownish deposits in the anterior eye segment, due to product accumulation, generally without effect on vision.

Investigations:

- Weight gain

Because of the sodium sulphite content there is a risk of allergic reactions, including anaphylactic reactions and bronchospasm.

Pregnancy, Puerperium and Perinatal Conditions:
Neonatal drug withdrawal syndrome (see Section 4.6) **-** *frequency not known.*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Extremely serious Parkinsonian syndrome, coma

Symptomatic treatment, continuous monitoring of respiratory and cardiac functions (risk of QT interval prolongation) should be maintained until the patient recovers (see Section 4.4).

Symptoms of levomepromazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, E.C.G. changes, ventricular arrhythmias, convulsions and hypothermia. Severe extra-pyramidal dyskinesias may occur.

If the 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 vasodilatation may result in circulatory collapse; raising the patients 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 tachy-arrhythmias 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 intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam. Neuroleptic malignant syndrome should be treated with cooling. Dantroline sodium may be tried.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics, ATC Code: N05AA02

Levomepromazine is a neuroleptic antipsychotic, aliphatic chain phenothiazine (N: central nervous system). Neuroleptic antipsychotics have antidopaminergic properties which are responsible for:

- The desired antipsychotic therapeutic effect
- The side effects (extrapyramidal syndrome, dyskinesia, Hyperprolactinaemia

Levomepromazine has moderate antidopaminergic activity, low antipsychotic activity and very moderate extrapyramidal effects. It resembles chlorpromazine and promethazine in the pattern of its pharmacology. It possesses anti-cholinergic, anti-histamine and anti-adrenaline activity and exhibits a strong sedative effect.

5.2 Pharmacokinetic properties

Peak plasma concentrations are reached on average 30-90 minutes after intramuscular injection. The half-life of Levomepromazine shows marked inter-individual variability (15 to 80 hours). Metabolites include sulfoxide derivatives and an active demethylated derivative. It is eliminated via urine and faeces.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic Acid
Sodium Sulphite Anhydrous (E221)
Sodium Chloride
Water for Injections

6.2 Incompatibilities

Incompatible with alkaline solutions.

6.3 Shelf life

Unopened: 36 months
Once opened, use immediately and discard any unused contents.

6.4 Special precautions for storage

Do not store above 25°C. Keep ampoule in the outer carton.

6.5 Nature and contents of container

Outer carton containing 10 glass ampoules of 2ml capacity containing 1ml of product.
Type I, colourless, Ph. Eur. glass ampoules with a 2ml capacity, containing 1ml of solution.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Nozinan injection may be diluted with an equal volume of normal saline immediately before use. Diamorphine hydrochloride is compatible with this solution and may be added if greater analgesia is required.
Diluted solutions are for single use and should be used immediately after preparation. Discoloured solutions should not be used.

7 MARKETING AUTHORISATION HOLDER

Neuraxpharm Ireland Limited
4045 Kingswood Road
Citywest
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23229/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 January 1983

Date of last renewal: 04 June 2006

10 DATE OF REVISION OF THE TEXT

November 2023