

SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NOZINAN 25 mg scored film coated tablets
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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nozinan 25mg

Levomepromazine maleate 33.8 mg
Quantity equivalent to levomepromazine base 25.0 mg
for one scored film-coated tablet.

For a full list of excipients, see Section 6.1

Nozinan 100mg

Levomepromazine maleate 135.0 mg
Quantity equivalent to levomepromazine base 100.0 mg
for one scored film-coated tablet.

For a full list of excipients, see Section 6.1

3. PHARMACEUTIC FORM

Scored film coated tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Neuroleptic drug

- Acute psychotic states.

Chronic psychotic states (schizophrenia, chronic non-schizophrenic delirium: paranoid delirium, chronic hallucinatory psychoses).

- In association with an antidepressant – short-duration treatment of certain severe forms of major depressive episodes.

This association can be done only during the initial period of the treatment, namely, during the period from 4 to 6 weeks,

4.2. Posology and method of administration

Not recommended for use in children

Oral route

The minimal efficient dosage should be always sought. The treatment should be started from a low dose and then gradually increasing it.

The dosage is from 25 to 200 mg/day.

In certain exceptional cases, the dosage can be increased to 400 mg/day maximum.

The daily dose should be either taken in the evening when going to bed, or distributed into three takings during meals.

4.3. Contraindications

This medicine is contraindicated in the following cases:

- hypersensitivity to levomepromazine or any of the other ingredients
- risk of angle-closure glaucoma

- risk of urinary retention related to urethro-prostatic disorders
- history of agranulocytosis
- allergy to wheat (other than celiac disease)
- in combination with:
 - dopamine agents excluding those used in Parkinson's disease (cabergoline, quinagolide) (see section 4.5)
 - dronedarone, mequitazine
 - certain severe cardiac diseases, in particular severe ischemic cardiac disease or heart failure

4.4. Special warnings and precautions for use

Warnings

- Each patient should be informed that in case of the appearance of fever, throat infection or any other infection, it is imperative to inform at once the attending physician and to control the hemogram immediately. In case of a downright modification of the latter (hyperleukocytosis, granulopenia), the administration of this treatment should be interrupted.

- Malignant syndrome: in case of unexplainable hyperthermia, it is imperative to suspend the treatment, because this sign can be one of the elements of the malignant syndrome described for neuroleptics (paleness, hyperthermia, vegetative disturbances, alteration of the conscience, muscular rigidity).

The signs of vegetative dysfunction, such as sweating and arterial instability, can precede the appearance of the hyperthermia and, consequently, constitute precocious signals.

Although this effect of neuroleptics can have an idiosyncratic origin, it seems that certain risk factors predispose to it, such as the dehydration or organic cerebral attacks.

- Lengthening of the QT interval: Neuroleptic phenothiazines may potentiate QT interval prolongation which increase the risk of onset of serious ventricular arrhythmias of the torsade de pointes type which is potentially fatal (sudden death). The levomepromazine lengthens the QT interval in a dose-dependent manner. This effect, which is known to potentiate the risk of the occurrence of grave ventricular rhythm disturbances of the torsades de pointes type, is increased due to the existence of a bradycardia, hypokalemia, a long congenital or acquired QT (association to a medicine increasing the QT interval). Therefore, it is appropriate before any administration, whenever

the clinical situation permits, to make sure of the absence of factors that can be favorable for the occurrence of this rhythm disturbance:

- bradycardia inferior to 55 beats per minute
- hypokalemia
- congenital lengthening of the QT interval
- current treatment with a medicine that is susceptible to cause a marked bradycardia (< 55 beats per minute), a hypokalemia, a slowing-down of the intracardiac conduction, a lengthening of the QT interval.

- Stroke: In randomized, placebo-controlled clinical trials in elderly patients with dementia and treated with certain atypical antipsychotics, a higher risk of stroke was observed versus placebo. The reason for this increased risk is unknown. Increased risk with other antipsychotics or in other patient populations cannot be ruled out. This drug must be used with caution in patients with risk factors for stroke.

- Elderly patients with dementia: the risk of mortality increases in elderly patients suffering from dementia-related psychosis and treated with antipsychotic drugs.

Analysis of 17 placebo-controlled studies (mean duration of 10 weeks), conducted in patients mainly taking atypical antipsychotic drugs, showed that the risk of mortality increased 1.6- to 1.7-fold in patients treated with these medicinal products versus placebo.

After a mean treatment period of 10 weeks, the risk of mortality was 4.5% in the treated patient group versus 2.6% in the placebo group.

Although the causes of death varied in the clinical trials with the atypical antipsychotic drugs, the majority of deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia).

Epidemiological studies suggest that treatment with conventional antipsychotic drugs may increase mortality, as is the case for atypical antipsychotic drugs.

The respective contribution of the antipsychotic drug and patient characteristics to the increase in mortality found in the epidemiological studies is unclear.

- Venous thromboembolism: cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotic drugs often present acquired risk factors for VTE, any potential risk factors for VTE must be identified before and during treatment with Nozinan and preventive measures should be taken (see Section 4.8).

- Except in special cases, this drug should not be administered to 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 necrotizing enterocolitis have been reported.

- It is inadvisable to use this drug in combination with alcohol, levodopa, dopamine antiparkinsonian drugs, antiparasitics likely to induce torsades de pointes, methadone, other neuroleptics and drugs likely to induce torsades de pointes (see Section 4.5).

- This medicinal product contains lactose. Its use is inadvisable in patients with galactose intolerance, Lapp lactase deficiency or glucose and galactose malabsorption syndrome (rare hereditary diseases).
- This medicinal product may be administered in patients with celiac disease. Wheat starch can contain gluten, but only traces, and is therefore considered safe for patients with celiac disease.

Precautions for use

The supervision of levomepromazine treatment should be strengthened:

- in epileptics because of the possibility of the epileptogenic threshold lowering. The occurrence of convulsive attacks makes it imperative to stop the treatment.
- in elderly patients with: an elevated sensitivity to an orthostatic hypotension, sedation and extrapyramidal effects.
- a chronic constipation (risk of paralytic ileus)
- an eventual prostatic hypertrophy
- in patients – carriers of certain cardiovascular affections because of the quinidinic tachycardiac and hypotensive effects of this class of products
- in case of severe hepatic and/or renal insufficiency because of the risk of accumulation

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).

Levomepromazine may lower epileptic threshold (see Sections 4.5 and 4.8) and should be used with caution in epileptic patients.

4.5. Interactions with other medicinal products and other forms of interaction

Cytochrome P450 2D6 Metabolism: Levomepromazine and its non-hydroxylated metabolites are reported to be potent inhibitors of cytochrome P450 2D6. Co-administration of levomepromazine and drugs primarily metabolised by the cytochrome P450 2D6 enzyme system may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic or adverse effects of those drugs

Drugs lowering the seizure threshold

Use of this drug in combination with seizure-inducing agents or seizure-threshold lowering drugs should be carefully considered due to the severity of the risk incurred. These drugs include in particular most antidepressants (imipramine agents, selective serotonin reuptake inhibitors), neuroleptics (phenothiazines and butyrophenones), mefloquine, chloroquine, bupropion, and tramadol.

Atropine-like drugs

It must be taken into account that atropine-like substances can have additive adverse effects and more easily lead to urinary retention, acute attacks of glaucoma, constipation, dry mouth, etc.

The various atropine-like drugs include imipramine antidepressants, most atropine-like H1-antihistamines, anticholinergic antiparkinsonians, atropine-like antispasmodics, disopyramide, phenothiazine neuroleptics, and clozapine.

Sedatives

It must be taken into account that many drugs or substances can have additive depressant effects on the central nervous system and contribute to a decrease in alertness. These drugs include morphine derivatives (analgesics, antitussives, and replacement therapies), neuroleptics, barbiturates, benzodiazepines, non-benzodiazepine anxiolytics (such as meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine), sedative H1-antihistamines, centrally-acting antihypertensives, baclofen, and thalidomide.

Drugs likely to induce torsades de pointes

This serious cardiac rhythm disorder can be caused by a certain number of antiarrhythmic and non-antiarrhythmic drugs. Hypokalemia (see Potassium-depleting drugs) is a promoting factor, as is bradycardia (see Bradycardia-inducing drugs) or pre-existing congenital or acquired QT interval prolongation.

The medicines involved are in particular class Ia and III antiarrhythmics and certain neuroleptics.

For dolasetron, erythromycin, spiramycin, and vincamine, only forms administered intravenously are concerned by this interaction.

Coadministration of two torsadogenic drugs is generally contraindicated. However, methadone, as well as certain sub-classes, are exceptions:

- antiparasitics (halofantrine, lumefantrine, pentamidine) are merely not recommended in combination with other torsadogenic drugs
- neuroleptics likely to induce torsades de pointes are also not recommended, but not contraindicated, in combination with other torsadogenic drugs

Contraindicated combination

see Section 4.3

- **dopamine agonists excluding those used in Parkinson's disease (cabergoline, quinagolide)**
Mutual antagonism between dopamine agonists and neuroleptics.

dronedarone, mequitazine

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

Inadvisable combinations

see Section 4.4

- **Other drugs likely to induce torsades de pointes: class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide) and class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide), and other drugs such as arsenic compounds bepridil, cisapride, diphemanil, dolasetron IV, erythromycin IV, mizolastine, vincamine IV, moxifloxacin, spiramycin IV, toremifen.**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

- **Other neuroleptics likely to induce torsades de pointes (amisulpride, chlorpromazine, cyamemazine, droperidol, flupentixol, fluphenazine, propericiazine, haloperidol, pimozide, pipotiazine, pipamperone, sertindole, sulpiride, sultopride, tiapride, zuclopenthixol)**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

- **Antiparasitics likely to induce torsades de pointes (halofantrine, lumefantrine, pentamidine)**

Increased risk of ventricular arrhythmias, particularly torsades de pointes. **If possible stop one of these two treatments.** If coadministration cannot be avoided, QT interval should be checked before treatment and the ECG monitored.

- **Alcohol**

Potiation of the sedative effects induced by neuroleptic drugs.

Impaired alertness may make driving vehicles and using machines dangerous.

Patients should not consume alcoholic beverages or medicinal products containing alcohol.

- **Levodopa**

Mutual antagonism between levodopa and neuroleptics.

In patients with Parkinson's disease, minimum effective doses of each of these drugs should be used.

- **Antiparkinsonian dopamine agonists (amantadine, apomorphine, bromocriptine, entacapone, lisuride, pergolide, priribedil, rasagiline, pramipexole, ropinirole, selegiline)**

Mutual antagonism between dopamine agonists and neuroleptics.

Dopamine agonists can cause or worsen psychotic disorders. If treatment with neuroleptics is required in patients with Parkinson's disease treated with dopamine agonists, these dopamine agents should be tapered off gradually (sudden discontinuation exposes the patient to a risk of neuroleptic malignant syndrome).

- **Methadone**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

Combinations requiring precautions for use

- **Beta blockers in heart failure (bisoprolol, carvedilol, metoprolol, nebivolol)**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

. In addition, vasodilator effect and risk of hypotension, particularly postural (additive effect).

Clinical and ECG monitoring required.

- **Bradycardia-inducing drugs (in particular class Ia antiarrhythmics, beta blockers, certain class III antiarrhythmics, certain calcium channel blockers, digitalis glycosides, pilocarpine, anticholinesterases)**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.
Clinical and ECG monitoring required.

- **Potassium-depleting drugs (potassium-depleting diuretics, alone or in combination, stimulant laxatives, glucocorticoids, tetracosactide and amphotericin B IV)**

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

Any existing hypokalemia should be corrected before administration, and clinical, electrolyte and ECG monitoring performed.

- **Azithromycin, clarithromycin, roxithromycin**

Increased risk of ventricular arrhythmias, particularly torsades de pointes. Clinical and ECG monitoring required during co-administration.

- **Lithium**

Risk of onset of neuropsychiatric symptoms suggestive of neuroleptic malignant syndrome or lithium poisoning. Regular clinical and laboratory monitoring (blood lithium levels) required, especially at the start of co-administration.

- **Topical agents for gastrointestinal use, antacids and adsorbent agents**

Decreased gastrointestinal absorption of phenothiazine neuroleptics.

Allow for an interval between administration of topical gastrointestinal agents, antacids and phenothiazine neuroleptics (more than 2 hours apart, if possible).

Combinations to be taken into account

- **Antihypertensives**

Increased risk of hypotension, particularly postural.

- **Beta blockers (except esmolol and sotalol and beta blockers used in heart failure)**

Vasodilator effect and risk of hypotension, particularly postural (additive effect).

- **Nitrates, nitrites and related drugs**

Increased risk of hypotension, particularly postural.

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- **Other drugs lowering the seizure threshold**

- **Increased risk of seizure.**

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- **Other atropine-like drugs**

- **Additive effects of atropine-like substances such as urinary retention, constipation, dry mouth, etc.**

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- **Other sedatives**
- **Increased central nervous system depression. Impaired alertness may make it dangerous to drive and use machines.**

4.6. Pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established

Good mental health should preferably be maintained throughout pregnancy to avoid decompensation. If drug therapy is necessary in order to maintain such a balance, it must be initiated or continued at an effective dose throughout pregnancy. Analysis of exposed pregnancies has not revealed any particular teratogenic effect with levomepromazine.

Newborns exposed to antipsychotic drugs (including Nozinan) during the third trimester of pregnancy are at risk for undesirable effects including extrapyramidal and/or withdrawal symptoms varying in severity and duration. The following reactions have been reported:

- respiratory disorders of varying degrees, ranging from tachypnea to respiratory distress, bradycardia, and hypotonia, usually occurring during co-administration with other medicinal products such as psychotropic or antimuscarinic drugs

signs related to the atropinic properties of phenothiazines such as tachycardia, hyperexcitability, abdominal distension, delayed meconium excretion, meconium ileus, feeding difficulties

neurological disorders such as extrapyramidal symptoms : hypertonia, tremor, agitation.

- sedation
- Consequently, newborns should be monitored carefully, taking into account the above-mentioned effects
- The medication should not be used during pregnancy unless the benefits outweigh the risks.

Lactation

As there are no data available on excretion in breast milk, breast-feeding is not recommended during treatment.

4.7. Effects on the ability to drive and use machines.

The attention, in particular, of vehicle drivers and users of machines is attracted to the risks of drowsiness connected with this medicine, especially in the beginning of the treatment.

4.8. Undesirable effects

At low doses

- Autonomic disturbances:
- postural hypotension,
- anticholinergic effects such as dry mouth, constipation, even paralytic ileus (see Section 4.4), visual accommodation disorders, risk of urinary retention (see Section 4.4).
- Neuropsychiatric disorders:
- sedation or drowsiness, more pronounced at the beginning of treatment,
- indifference, anxiety reactions, mood changes.
- **At higher doses**
- Neuropsychiatric disorders:
- early-onset dyskinesia (spasmodic torticollis, oculogyric crises, trismus, etc.).
- extrapyramidal syndrome:
 - o akinetic symptoms with or without hypertonia, partially resolving with anticholinergic antiparkinsonian agents,
 - o hyperkinetic-hypertonic and excitatory motor activity,
 - o akathisia
- tardive dyskinesia, occurring particularly during long-term treatment. It may sometimes occur after the neuroleptic agent is withdrawn and resolve after rechallenge or if dosage is increased.
- Anticholinergic antiparkinsonians have no effect and may cause exacerbation.
- Autonomic disturbances:
- anticholinergic effects: very rare cases of potentially fatal necrotizing enterocolitis have been reported (see Section 4.4).
- Endocrine and metabolic disorders:
- hyperprolactinemia: amenorrhea, galactorrhea, gynecomastia, impotence, frigidity,
- thermoregulation disorders,
- weight gain,
- hyperglycemia, impaired glucose tolerance. (see section 4.4)
- **Dose-dependent and rarely reported**
- Cardiac disorders:
- QT interval prolongation,
- very rare cases of torsades de pointes have been reported.
- **Non-dose-dependent and more rarely reported**
- Skin disorders:
- allergic skin reactions,

- photosensitization.
- Blood disorders:
- exceptional cases of agranulocytosis: regular differential leukocyte counts are recommended,
- leukopenia.
- Eye disorders:
- brownish deposits in the anterior segment of the eye caused by accumulation of the drug and generally without effect on vision.
- Other disorders:
- positive titer for antinuclear antibodies in patients who do not have clinical lupus erythematosus,
- neuroleptic malignant syndrome (see Section 4.4),
- possible cholestatic jaundice,
- very rare cases of priapism.

In addition, isolated cases of sudden death of cardiac origin and unexplained sudden death have been reported in patients treated with phenothiazine, butyrophenone or benzamide antipsychotic neuroleptics (see Section 4.4).

Cases of venous thromboembolism, including cases of pulmonary embolism and deep vein thrombosis, have been reported with antipsychotics - unknown frequency (see Section 4.4).

Additional adverse events reported:

Nervous system disorders: Confusional states, delirium, convulsions

Hepatobiliary disorders: Hepatocellular, cholestatic and mixed liver injury.

Metabolism and nutrition disorders: hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

4.9 Overdose

Extremely serious parkinsonian syndrome, coma, convulsions.

Symptomatic treatment, continuous respiratory and cardiac supervision (risk of the lengthening of QT interval), which should be continued until the recovery of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ANTIPSYCHOTICS

ATC code: N05AA02

(N: Central Nervous system)

Neuroleptic antipsychotics have antidopamine properties which are responsible for:

- the desired antipsychotic therapeutic effect,
- the side effects (extrapyramidal syndrome, dyskinesia and hyperprolactinemia).

This antidopamine activity is moderate with levomepromazine: it has low antipsychotic activity and very moderate extrapyramidal effects.

The compound also exhibits antihistamine properties (causing sedation, generally a desired clinical effect), as well as marked adrenolytic and anticholinergic properties.

5.2 Pharmacokinetic properties

Peak plasma concentrations are reached on average 1 to 3 hours after oral dosing.

Bioavailability is 50%.

The half-life of levomepromazine shows marked interindividual variability (15 to 80 hours).

The metabolites of levomepromazine include sulfoxide derivatives and an active demethylated derivative.

The drug is eliminated via the urinary and fecal routes.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, wheat starch, hydrated silica colloidal, dextrin, magnesium stearate, hypromellose, macrogol 20 000.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Store below 25°C. Protect from light.

7. MANUFACTURER

Famar Lyon France

8. MARKETING AUTHORIZATION HOLDER

Sanofi-aventis Israel Ltd.