ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nozinan 100 mg scored film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Levomepromazine maleate acid .....135.0 mg

Equivalent to levomepromazine base .....100.0 mg

For one scored film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Scored film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Acute psychotic disorders.

Chronic psychotic disorders (schizophrenia, chronic non-schizophrenic delusions: paranoid delusions, chronic hallucinatory psychosis).

- In combination with an antidepressant, short-term treatment of certain severe forms of major depression.

This drug combination may only be used during the initial period of treatment, i.e. for 4 to 6 weeks.

4.2. Posology and method of administration

Posology

For use in adults only.

Oral use.

The minimum effective dose should be used in all cases. Treatment should be initiated at a low dose, then gradually increased.

The daily dose is 25 to 200 mg.

In some exceptional cases, the dose may be increased to a maximum of 400 mg per day.

The daily dose should be taken either in the evening at bedtime or in 3 divided doses at mealtimes.

4.3. Contraindications

- Hypersensitivity to levomepromazine or any of the excipients,
- Risk of closed-angle glaucoma,
- Risk of urinary retention related to urethraprostatic disorders,
- History of agranulocytosis,
- In combination with:
  - non-antiparkinsonian dopamine agonists (cabergoline, quinagolide),
  - citalopram, escitalopram,
  - hydroxyzine,
  - piperaquine,
  - domperidone.
- In patients with a wheat allergy (other than celiac disease).

4.4. Special warnings and precautions for use

Special warnings

All patients must be informed 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

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discontinued if any marked changes (hyperleukocytosis, 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 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.

Prolonged QT interval: Levomepromazine can prolong the QT interval dose-dependently. This effect, which is known to increase the risk of onset of serious ventricular arrhythmias, particularly torsades de pointes, is exacerbated in the presence of bradycardia, hypokalemia and congenital or acquired QT prolongation (when levomepromazine is taken with a medicinal product prolonging the QT interval) (see section 4.8). Consequently, before administering the drug and if the clinical situation permits, the physician should make sure that there are no risk factors that may promote this type of arrhythmia, i.e.:

- bradycardia of less than 55 beats per minute,
- hypokalemia,
- congenital QT interval prolongation,
- ongoing treatment with a drug likely to cause marked bradycardia (< 55 beats per minute), hypokalemia, 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.

Stroke: In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotics, a higher risk of cerebrovascular events has been observed versus placebo. The mechanism of such risk increase is unknown. An increase in the risk with other antipsychotic drugs or other patients cannot be excluded. This drug 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 increased risk of death.
Analyses of 17 placebo-controlled studies (mean duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients between 1.6 to 1.7 times the risk of death in placebo-treated patients.
Over the course of a mean 10-week treatment period, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.
Although the cause of death in clinical trials with atypical antipsychotic drugs were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious in nature (e.g. pneumonia).
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 antipsychotic drugs. Since patients treated with antipsychotic drugs often have 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).

Apart from exceptional cases, this drug should not be used in patients with Parkinson's disease.

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

Very rare cases of potentially fatal necrotizing enterocolitis have been reported.

It is not recommended to use this drug in combination with alcohol, levodopa, dopaminergic antiparkinsonism agents, 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. Patients with galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption syndrome (rare hereditary diseases).should not take this medicinal product

This medicinal product can be administered in patients with celiac disease. Wheat starch can contain gluten, but only trace amounts, and is therefore considered safe for these patients.

Precautions for use

Careful monitoring of treatment with levomepromazine is required in

- Epileptic patients, as levomepromazine may lower the seizure threshold. Treatment must be discontinued if seizures occur,
- Elderly patients with:
  - greater susceptibility to orthostatic 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 impairment and/or renal impairment, due to the risk of accumulation.

Hyperglycemia or intolerance to glucose and onset or exacerbation of diabetes have been reported in patients treated with phenothiazines (see section 4.8).

Patients receiving treatment with antipsychotic drugs, including **Nozinan**, should undergo clinical and laboratory monitoring that complies with current recommendations. Particular caution should be exercised in patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes.

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

Seizure threshold-lowering drugs

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

Atropine-like substances

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 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 medicinal products that induce this adverse effect include class Ia and III antiarrhythmic agents and certain neuroleptics.

Other compounds not belonging to these classes are also involved.

For dolasetron, erythromycin, spiramycin and vincamine, this interaction is only likely with intravenous forms.

Coadministration of two torsadogenic drugs is generally contraindicated.

However, this does not apply to some of these agents which are considered absolutely necessary and are therefore simply not recommended in combination with other torsadogenic medicinal products. These include methadone, hydroxychloroquine, antiparasitic drugs (chloroquine, halofantrine, lumefantrine, pentamidine) and neuroleptics.
Citalopram, escitalopram, domperidone, hydroxyzine and piperaquine, on the other hand, are not among these exceptions, and are therefore contraindicated with all torsadogenic drugs.

Drugs inducing orthostatic hypotension

In addition to antihypertensive agents, numerous drugs may cause orthostatic hypotension. These include nitrates, phosphodiesterase type-5 inhibitors, alpha-blocking agents for urological purposes, imipramine antidepressants and phenothiazine neuroleptics, dopamine agonists and levodopa. Concomitant use could therefore increase the frequency and intensity of this adverse effect. Refer to the interactions specific to each class, with the corresponding obligations.

Contraindicated combinations (see section 4.3)

+ Non-antiparkinsonian dopamine agonists (cabergoline, quinagolide)

There is a mutual antagonism between dopamine agonists and neuroleptics.

+ Citalopram, escitalopram

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Hydroxyzine

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Piperaquine

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Domperidone

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

Inadvisable combinations (see section 4.4)

+ Other neuroleptics likely to induce torsades de pointes (amisulpride, chlorpromazine, cyamemazine, droperidol, flupenthixol, fluphenazine, haloperidol, pimozide, pipotiazine, pipamperone, sulpiride, sultopride, tiapride, zuclopenthixol)

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Antiparasitics likely to induce torsades de pointes (chloroquine, halofantrine, lumefantrine, pentamidine)

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

If possible, one of the two treatments should be discontinued. If coadministration cannot be avoided, QT interval should be checked before treatment and the ECG monitored.

+ Medicinal products likely to induce torsades de pointes (except for antiparasitics, neuroleptics and methadone; see "Inadvisable combinations"):

- class Ia antiarrhythmic agents (quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmic agents (amiodarone, sotalol),
- other medicinal products such as: arsenic compounds, diphemanil, dolasetron IV, dronedarone, erythromycin IV, mequitazine, mizolastine, moxifloxacin, prucalopride, spiramycin IV, toremifene, vandetanib, vincamine IV.

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Alcohol (beverage or excipient)

Alcohol potentiates the sedative effects induced by neuroleptics.

Impaired alertness may be hazardous for driving vehicles and using machines.

Use of alcoholic beverages or medicinal products containing alcohol should be avoided.

+ **Levodopa**

There is a 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, piribedil, pramipexole, rasagiline, ropinirole, rotigotine, selegiline, tolcapone)**

There is a 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, the dopamine agents should be tapered off gradually (sudden discontinuation exposes the patient to a risk of neuroleptic malignant syndrome).

+ **Methadone**

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ **Hydroxychloroquine**

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ **Sodium (oxybate)**

Sodium oxybate potentiates the CNS depressant effect of the drug. Impaired alertness may be hazardous for driving vehicles and using machines.

Combinations requiring precautions for use

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

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

Coadministration can cause a vasodilator effect and risk of hypotension, particularly orthostatic (additive effect).

Clinical and ECG monitoring is required.

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

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

Clinical and ECG monitoring is required.

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

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

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

+ **Azithromycin, clarithromycin, roxithromycin**

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

Clinical and ECG monitoring is required during coadministration.

+ **Ciprofloxacin, levofloxacin, norfloxacin**

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

Clinical and ECG monitoring is required during coadministration.

+ **Lithium**

There is a risk of developing neuropsychiatric symptoms suggestive of a neuroleptic malignant syndrome or lithium poisoning.

Regular clinical and laboratory (blood lithium) monitoring is required, particularly at the start of coadministration.

+ Topical agents for gastrointestinal use, antacids and adsorbent agents

There is decreased gastrointestinal absorption of phenothiazine neuroleptics.

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

+ Ondansetron

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

Clinical and ECG monitoring is required during coadministration.

+ Anagrelide

There is an increased risk of ventricular arrhythmias, particularly torsades de pointes.

Clinical and ECG monitoring is required during coadministration.

Combinations to be taken into account

+ Other drugs lowering the seizure threshold

There is an increased risk of seizures.

+ Other atropine-like drugs

Additive effects caused by atropine-like substances (e.g. urinary retention, constipation and dry mouth) may occur.

+ Other sedatives

Sedatives potentiate the CNS depressant effect of the drug. Impaired alertness may be hazardous for driving vehicles and using machines.

+ Dapoxetine

There is a risk of increased adverse effects, particularly dizziness or syncope.

+ Blood pressure-lowering drugs

There is a risk of increased hypotension, particularly orthostatic.

+ Orlistat

There is a risk of treatment failure if administered concomitantly with orlistat.

4.6. Fertility, pregnancy and lactation

Pregnancy

Good mental health should be maintained throughout pregnancy to avoid any decompensation. If drug treatment is necessary to maintain such a balance, it must be initiated or continued at an effective dose throughout therapy.

Neonates exposed to antipsychotics (including **Nozinan**) during the third trimester of pregnancy are at risk for adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. Agitation, hypertonia, hypotonia, tremor, drowsiness, respiratory distress and feeding disorders have been reported.

Clinical data on levomepromazine are reassuring but still limited, and available data from animal studies are insufficient to determine reproductive toxicity.

Given these data, and as a precaution, the use of **Nozinan** is not recommended during pregnancy. Close monitoring of neonates born to mothers receiving treatment at the end of pregnancy is necessary.

Breast-feeding

Levomepromazine is excreted in human breast milk. A risk to the suckling child cannot be excluded.

Breast-feeding is not recommended during treatment.

Fertility

There are no fertility data in animals.

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In humans, because of the interaction with dopamine receptors, levopromazine may cause hyperprolactinemia which can be associated with impaired fertility in women and/or men.

4.7. Effects on ability to drive and use machines

The attention of patients, particularly those who drive or operate machinery, should be drawn to the risk of drowsiness associated with this medicinal product, particularly at the beginning of treatment.

4.8. Undesirable effects

At low doses:

Autonomic disorders:

- orthostatic hypotension,
- anticholinergic effects such as dry mouth, constipation and even paralytic ileus, 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:
  - akinetic symptoms with or without hypertonia, partially resolving with anticholinergic antiparkinsonian agents,
  - hyperkinetic-hypertonic and excitatory motor activity,
  - akathisia.
- tardive dyskinesia, occurring during long-term treatment. Tardive dyskinesia may occur after the neuroleptic is withdrawn and resolve after rechallenge or if the dose is increased.

Anticholinergic antiparkinsonians have no effect and may cause exacerbation.

Autonomic disorders:

- 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, diabetes, impaired glucose tolerance (see section 4.4).

Dose-dependent and rarely reported:

Cardiac disorders:

- prolongation of the QT interval,
- 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 with no effect on vision.

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Hepatobiliary disorders:

- elevated transaminase levels, cholestatic jaundice, cholestatic, cytolytic and mixed hepatitis.

Other disorders:

- positive titer for antinuclear antibodies in patients who do not have clinical lupus erythematosus,
- neuroleptic malignant syndrome (see section 4.4),
- very rare cases of priapism.

In addition, there have been isolated reports of sudden death of cardiac origin as well as cases of unexplained sudden death, in patients receiving 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 (see section 4.4). The frequency of these events is not known.

Pregnancy, puerperium and perinatal conditions: neonatal withdrawal syndrome (see section 4.6). The frequency of these events is not known.

Nervous system disorders: confusion and seizures. The frequency of these events is not known.

Metabolism and nutrition disorders: hyponatremia and inappropriate antidiuretic hormone secretion syndrome (SIADH). The frequency of these events is not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 the French national reporting system, i.e. *Agence Nationale de Sécurité du Médicament et des Produits de Santé* (ANSM) under "*réseau des Centres Régionaux de Pharmacovigilance*" (network of Regional Pharmacovigilance Centers) - Website: www.ansm.sante.fr

4.9. Overdose

Seizures, extremely serious parkinsonian syndrome, coma.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: ANTIPSYCHOTIC, ATC code: N05AA02.

Neuroleptic antipsychotics have antidopamine properties which cause:

- the desired antipsychotic therapeutic effect,
- the following side effects: extrapyramidal syndrome, dyskinesia and hyperprolactinemia.

This antidopamine activity is moderate with levomepromazine: the compound 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 is characterized by marked interindividual variability (15 to 80 hours).

Levomepromazine metabolites include sulfoxide derivatives and an active demethylated derivative.

The drug is eliminated via the urinary and fecal routes.

5.3. Preclinical safety data

Available data show no teratogenic effect in rats following oral administration of up to 27 mg/kg/day (corresponding to an equivalent human dose of 1.3 times the maximum oral therapeutic dose of 200 mg/day).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose, wheat starch, hydrated silica, white dextrin, magnesium stearate, hypromellose, polyethylene glycol 20 000 (PEG 20 000), titanium oxide, yellow iron oxide.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 25 °C.

6.5. Nature and contents of container

20 tablets in (PVC-Aluminum) blisters.

6.6. Special precautions for disposal and other handling

Any unused medicinal products or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Sanofi aventis France
82, avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORIZATION NUMBER

- 34009 307 429-8 3: 20 tablets in (PVC-Aluminum) blisters.

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: {DD month YYYY}

Date of last renewal: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

[to be filled in subsequently by the MA Holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I.