PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**NOZINAN®**

Methotrimeprazine Hydrochloride Injection, USP

Solution, 25 mg/mL methotrimeprazine as methotrimeprazine hydrochloride, intravenous and intramuscular

USP

Neuroleptic

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RECENT MAJOR LABEL CHANGES

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1 INDICATIONS, 1.2 Geriatrics	09/2022
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NOZINAN (methotrimeprazine hydrochloride injection) is indicated for:

- Psychotic disturbances: acute and chronic schizophrenias, senile psychoses, manic-depressive syndromes.
- Analgesic: In pain due to cancer, zona, trigeminal neuralgia, neurocostal neuralgia, in phantom limb pains, muscular discomforts and as post-operative analgesic adjunct.
- Antiemetic: For the treatment of nausea and vomiting of central origin.
- Sedative: For the management of insomnia.

1.1 Pediatrics

Pediatrics (<1 year of age): Contraindicated See 2 CONTRAINDICATIONS.

Pediatrics (1 – 18 years of age): 4.2 4.2 Recommended Dose and Dosage Adjustment

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7 WARNINGS AND PRECAUTIONS, 4.2 4.2 Recommended Dose and Dosage Adjustment

NOZINAN is not indicated for the treatment of patients with dementia. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

2 CONTRAINDICATIONS

NOZINAN is contraindicated in children younger than 1 year, due to a possible association between use of phenothiazine-containing products and Sudden Infant Death Syndrome (SIDS).

NOZINAN (methotrimeprazine hydrochloride injection) is contraindicated in patients with:

- hypersensitivity to methotrimeprazine, other phenothiazines, or to any other ingredient in the formulation or component of the container;
- concomitant neuroleptics including dopaminergics;
- coma or CNS depression due to alcohol, hypnotics, analgesics or narcotics;
- blood dyscrasia, including agranulocytosis;
- bone marrow depression;
- hepatic impairment;
- brain damage;
- pheochromocytoma;
- circulatory collapse/severe hypotension, or severe heart disorder;
- myasthenia gravis;
- regional or spinal anesthesia;
- risk of urinary retention related to urethroprostatic disorders;
- risk of closed angle glaucoma.;

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Patients with dementia: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to those treated with placebo. See 7 WARNINGS AND PRECAUTIONS, and 7.1.4 Special Populations, Geriatrics.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

In high parenteral doses, orthostatic hypotension may be encountered at the start of treatment. Patients whose treatment is started by the parenteral route should be kept in bed during the first few days.

Patients should remain lying down for at least one hour after injection due to risk of hypotension (see 4.2 4.2 Recommended Dose and Dosage Adjustment).

Medical and laboratory evaluations should be performed prior to initiation of treatment, to rule out cardiovascular risk factors (in particular ventricular arrhythmia and QT prolongation) (see 7 WARNINGS AND PRECAUTIONS and 8.5 Post-Market Adverse Reactions).

NOZINAN therapy should be initiated at low doses in patients with arteriosclerosis or cardiovascular problems.
Careful monitoring of treatment with methotrimeprazine is required in patients with certain cardiovascular diseases, due to the quinidine-like, tachycardia inducing and hypotensive effects of this product class (see 7 WARNINGS AND PRECAUTIONS and 5 OVERDOSAGE).

All potential risk factors for venous thromboembolism (VTE) should be identified and preventive measures undertaken prior to initiation of treatment with NOZINAN (see 7 WARNINGS AND PRECAUTIONS and 8.2 Clinical Trial Adverse Reactions).

Because of its anticholinergic effects, NOZINAN must be administered with caution in patients with glaucoma and prostatic hypertrophy.

During long-term therapy, periodic liver function tests should be performed. In addition, complete blood counts (CBC) should be conducted regularly and physicians should watch for any signs of blood dyscrasia.

NOZINAN should be used with caution in epileptic patients, since phenothiazines, including NOZINAN, may lower the seizure threshold (see 7 WARNINGS AND PRECAUTIONS, Seizures 8 ADVERSE REACTIONS). It is advisable to administer an appropriate anticonvulsant medication to epileptic patients receiving NOZINAN therapy.

Careful monitoring of patients with severe renal impairment is recommended, due to the risk of accumulation.

Patients should have baseline and periodic monitoring of blood glucose and body weight.

Because of the risk of photosensitization, patients should be advised to avoid exposure to direct sunlight.

Patients are strongly advised not to consume alcoholic beverages or to take medicines containing alcohol during treatment with NOZINAN.
Phenothiazines may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, general anesthetics, or alcohol.

4.2 Recommended Dose and Dosage Adjustment

Dosage must be adjusted according to the indication and individual needs of the patient. If sedation during the day is too pronounced, lower doses may be given during the day and higher doses at night. Patients should remain lying down for at least one hour after injection, due to the risk of hypotension.

Adults

I.M.: 75 to 100 mg total daily dose, to be divided as a 25 mg injection given by deep I.M. injection in a large muscle 3 or 4 times per day. When given as a post-operative analgesic adjunct, the average dose varies from 10 to 25 mg every 8 hours, which is equivalent to 20 to 40 mg given orally. If NOZINAN is administered in conjunction with narcotics, the doses of the latter must be appropriately reduced.

Children

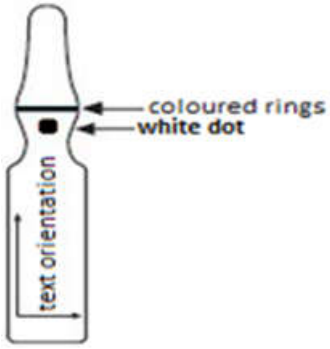
I.M.: A total daily dose of 0.0625 to 0.125 mg/kg, given once daily or in divided doses. Oral medication should be substituted as soon as possible.

I.V.: in the context of palliative care, 0.0625 mg/kg/day in 250 mL of a 5% glucose solution may be administered as a slow infusion (20 to 40 drops per minute).

4.3 Administration

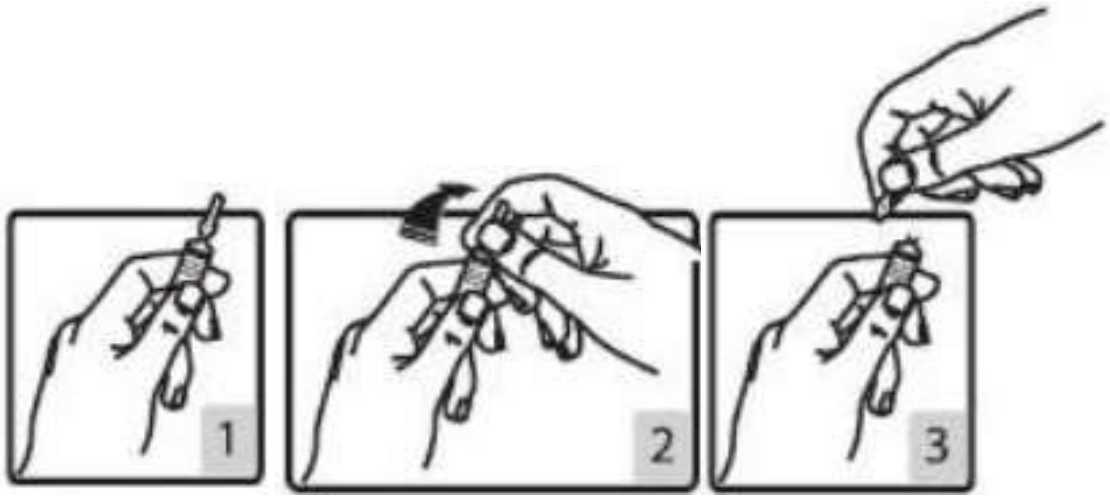
Do not use if solution shows haziness, particulate matter, discolouration, or leakage.

Ampoule opening instructions
NOZINAN ampoules are equipped with a weak spot in the glass stem, below the white dot, to facilitate opening the ampoule without excessive force.



- Hold the bottom part of the ampoule upright with one hand. If there is liquid in the top or stem of the ampoule, gently tap the top to move it to the bottom of the ampoule.

- Position the ampoule as indicated in Picture 1, with your thumb at or below the stem, pointing towards the white dot. Do not exert excessive pressure on the cylinder of the ampoule.
- With the other hand, grasp the top of the ampoule, positioning the thumb on the white dot at the top of the ampoule as indicated in Picture 2. Correct thumb position will target pressure on the break point (stem) of the ampoule just below the white dot.
- Using the thumb on the white dot, gently push the dot away from you (as indicated by the arrow in Picture 2) while applying counter pressure with the index finger of the same hand (pivot). Your two hands:
  - must not move apart (tearing action),
  - must not move closer to each other and
  - must not twist.



4.4 Missed Dose

If a dose is missed, it should be taken promptly, unless it is near the time of the next dose, in which case the missed dose should be skipped. The next dose should be taken at the regular time. Doses should not be doubled.

5 OVERDOSAGE

High doses cause depression of the central nervous system, presenting as lethargy, dysarthria, ataxia, stupor, reduction in consciousness into coma, convulsions; mydriasis; cardiovascular symptoms (related to risk of QT interval prolongation), such as hypotension, ventricular tachycardia and arrhythmia; respiratory depression; hypothermia. These effects may be potentiated by other medicines or by alcohol. Anticholinergic syndrome may occur. Severe parkinsonian syndrome may occur.

Symptoms: Symptoms of acute intoxication may include: simple CNS depression, spasms, tremor or tonic and clonic convulsions, coma accompanied by hypotension and respiratory depression.

Treatment: There is no specific antidote. After gastric lavage, treatment is symptomatic. Centrally acting emetics are ineffective because of the anti-emetic action of NOZINAN.

Hypotension: A 5% glucose solution may be administered. If a hypertensive agent is required, norepinephrine or phenylephrine may be used, but not epinephrine, which can aggravate hypotension.

Respiratory depression: Oxygen by inhalation or controlled respiration after tracheal intubation.

Respiratory infection: Wide spectrum antibiotics.

Extrapyramidal reactions: An antiparkinsonian agent or chloral hydrate, however the latter must be used with caution because of its depressant effect on respiration.

Any CNS stimulant should be used with caution.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous (IV) Intramuscular (IM)	Each mL contains: methotrimeprazine base 25 mg (as the hydrochloride)	0.1% ascorbic acid, 0.65% sodium chloride, 0.05% sodium sulfite and water for injection.

NOZINAN (methotrimeprazine base) 25 mg/mL (as hydrochloride) injectable is available in amber glass ampoules of 1 mL in boxes of 10 ampoules.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Acute withdrawal symptoms, including nausea, vomiting, headache, anxiety, agitation, dyskinesia, dystonia, disturbed temperature regulation, and insomnia, have very rarely been reported following the abrupt cessation of high doses of neuroleptics.
Relapse may also occur, and the emergence of extrapyramidal reactions has been reported. Therefore, gradual withdrawal is advisable. Symptoms of withdrawal can occur following treatment at any dose. Withdrawal of treatment should occur under close medical supervision.

Body Temperature Regulation:

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing NOZINAN for patients who will be experiencing conditions which may contribute to an elevation of core temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Elderly Patients:

NOZINAN should be avoided in patients with Parkinson's disease.

NOZINAN is not indicated for the treatment of patients with dementia see 7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics.

Careful monitoring of treatment with methotrimeprazine is required when administered in elderly patients exhibiting greater susceptibility to orthostatic hypotension, sedation, and extrapyramidal effects; chronic constipation (risk of ileus paralytic); possible prostatic hypertrophy.

NOZINAN should be used cautiously in the elderly owing to their susceptibility to drugs acting on the central nervous system and a lower initial dosage is recommended. There is an increased risk of drug-induced Parkinsonism in the elderly particularly after prolonged use.

NOZINAN should be used with caution in the elderly, particularly during very hot or very cold weather (risk of hyper-, hypothermia).

Cardiovascular

NOZINAN should be avoided in patients with cardiac failure.

Hypotension: Hypotension, which is typically orthostatic, may occur, especially in elderly and in alcoholic patients. This effect may be additive with other hypotensive agents. Exercise special care in those patients in whom a hypotensive crisis would be undesirable, such as those with arteriosclerosis or other cardiovascular diseases.

QT Interval: As with other neuroleptics, very rare cases of QT interval prolongation have been reported with NOZINAN. 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 8 ADVERSE REACTIONS and 9 DRUG INTERACTIONS.

NOZINAN should be used with caution in patients with risk factors for stroke or with a history of stroke as well as patients with risk factors for thromboembolism.

Dependence/Tolerance

In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea, vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy.

Driving and Operating Machinery

NOZINAN, like other antipsychotics, has the potential to impair judgement, thinking, or motor skills.

Patients should be warned about drowsiness, dizziness, and blurred vision and advised not to drive or operate machinery, particularly during the early days of treatment, until they know how NOZINAN affects them.

Endocrine and Metabolism

NOZINAN should be avoided in patients with hypothyroidism or pheochromocytoma.

Hyperglycemia: Hyperglycemia or intolerance to glucose has been reported in patients treated with NOZINAN. Diabetic ketoacidosis (DKA) has occurred in patients with no reported history of hyperglycemia. Patients should have baseline and periodic monitoring of blood glucose and body weight.

Hyperprolactinemia: Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

Gastrointestinal
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 life-threatening necrotizing colitis have been reported (see 8 ADVERSE REACTIONS).

Genitourinary
Rare cases of priapism have been reported with antipsychotic use, such as NOZINAN. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment. The most likely mechanism of action of priapism is a relative decrease in sympathetic tone.

Hematologic

NOZINAN should be avoided in patients with agranulocytosis.

Blood disorders:

Neutropenia, granulocytopenia and agranulocytosis have been reported during antipsychotic use. Therefore, it is recommended that patients have their complete blood count (CBC) tested prior to starting NOZINAN and then periodically throughout treatment. Most cases of agranulocytosis associated with the administration of phenothiazine derivatives have occurred between the fourth and tenth week of treatment. Therefore, observe patients on prolonged therapy with particular care during that time for the appearance of such signs as sore throat, fever and weakness. The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see 8 ADVERSE REACTIONS), and requires immediate hematological investigation.

Vascular disorders:

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 8 ADVERSE REACTIONS).

In randomized, placebo-controlled, clinical trials placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increased risk of cerebrovascular events has been observed. The mechanism of this 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 (see 7.1.4 Geriatrics (≥ 65 years of age):)

Hepatic

NOZINAN should be avoided in patients with liver dysfunction.

Immune

NOZINAN should be avoided in patients with myasthenia gravis.

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 (hyperleukocytosis, granulocytopenia) are observed in the blood count.

Hypersensitivity reactions including urticaria and angioedema have been reported with NOZINAN use. In case of allergic reaction, treatment with NOZINAN must be discontinued and appropriate symptomatic treatment initiated (see 8 ADVERSE REACTIONS).

Monitoring and Laboratory Tests

The following assessments should be done before and periodically during treatment with NOZINAN.

- Blood glucose and body weight
- Complete blood count (CBC)
- WBC and differential counts and liver function tests
- Sore throat, fever and weakness in patients on prolonged therapy may indicate agranulocytosis. If these symptoms appear, discontinue the drug and perform liver function tests
- Blood pressure
- Renal function

Neurologic

Neuroleptic Malignant Syndrome:

A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with antipsychotic drugs, including NOZINAN.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue NOZINAN and provide intensive symptomatic treatment and monitoring.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs, including NOZINAN, and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Parkinson's Disease:
Apart from exceptional situations, NOZINAN should not be used in patients with Parkinson's Disease.

Tardive Dyskinesia: (See also 8.2 Central Nervous System)

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with conventional antipsychotic drugs. Although the prevalence of tardive dyskinesia with conventional antipsychotics appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the beginning of treatment, which patients are likely to develop the syndrome.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn.

Antipsychotic drug treatment itself, however, may suppress (or partially suppress) the signs and symptoms of tardive dyskinesia and thereby may possibly mask the underlying process.

The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

NOZINAN should be prescribed in a manner that is most likely to minimize the risk of tardive dyskinesia. The lowest effective dose and the shortest duration of treatment should be used, and treatment should be discontinued at the earliest opportunity, or if a satisfactory response cannot be obtained. If the signs and symptoms of tardive dyskinesia appear during treatment, discontinuation of NOZINAN should be considered.

Ophthalmologic

NOZINAN should be avoided in patients with a history of narrow angle glaucoma.

Phenothiazines have been associated with retinopathy and lenticular or corneal deposits. Discontinue NOZINAN if retinal changes are observed.

Peri-Operative Considerations

Psychotic patients on large doses of a phenothiazine drug who are undergoing surgery should be watched carefully for possible hypotensive phenomena. Moreover, it should be remembered that

reduced amounts of anesthetics or CNS depressants may be required.

Renal

NOZINAN should be avoided in patients with renal dysfunction or prostate hypertrophy.

Monitor the renal function of patients on long-term therapy with NOZINAN, due to the risk of accumulation. If abnormal values are observed, discontinue the drug. Patients who may develop urinary retention should be carefully observed. This drug should not be used in patients with renal insufficiency.

Reproductive Health: Female and Male Potential

- **Fertility**

There are no fertility data in animals. In humans, because of the interaction with dopamine receptors, NOZINAN may cause hyperprolactinemia which can be associated with impaired fertility in women. Some data suggest that NOZINAN treatment is associated with impaired fertility in men.

- **Teratogenic Risk**

Non-teratogenic effects:

Neonates exposed to antipsychotic drugs including NOZINAN during the third trimester of pregnancy are at risk for:

- neurological disorders such as extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence.
- various degrees of respiratory disorders ranging from tachypnoea to respiratory distress and bradycardia. Although these events occurred most often when other drugs such as psychotropic or antimuscarinic drugs were coadministered, they may also occur with antipsychotic use alone.
- signs related to atropinic properties of phenothiazines such as meconium ileus, delayed meconium passage, abdominal bloating, tachycardia and initial feeding difficulties in neonates can also occur.

These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. Appropriate monitoring and treatment of neonates born to mothers receiving NOZINAN are recommended.

Congenital malformations:
Animal studies are insufficient with respect to reproductive toxicity. Most studies indicate that these agents are not teratogenic but there are reports of defects in infants exposed to these drugs in utero during the first trimester. Risk of congenital malformations cannot be excluded.

Seizures
NOZINAN should be used with caution in epileptic patients, since phenothiazines, including NOZINAN, may lower the seizure threshold. It is advisable to administer an appropriate anticonvulsant medication to epileptic patients receiving NOZINAN therapy.

Sensitivity/Resistance

Phenothiazines like NOZINAN may impair sensitivity and adaptation to changes of environmental temperature so that fatal hyperthermia and heat strokes are possible complications.

Skin
Photosensitivity may occur. Patients should use sunscreens when exposed to sunlight for prolonged periods of time.

7.1 Special Populations

7.1.1 Pregnant Women

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 to the fetus.

7.1.2 Breast-feeding

Lactation:
Phenothiazines, including NOZINAN, are excreted in milk, therefore, breastfeeding is not recommended during treatment with NOZINAN. See 2 CONTRAINDICATIONS

7.1.4 Geriatrics (≥ 65 years of age):

Paralytic ileus, even resulting in death, may occur, appropriate measures should be taken if constipation develops.

NOZINAN is not indicated for the treatment of elderly patients with dementia-related psychosis.

Mortality in Geriatric Patients with Dementia-related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
In a meta-analysis of 13 controlled clinical trials, elderly patients with dementia treated with atypical antipsychotic drugs had an increased risk of mortality compared to placebo.

Observational studies suggest that, similar to atypical antipsychotics, 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.

Cerebrovascular Adverse Events (CVAEs) including stroke in Elderly Patients with Dementia

A 3-fold increase in risk of cerebrovascular adverse events has been seen in the dementia population in randomized clinical trials versus placebo with some atypical antipsychotics. The mechanism for this increased risk is not known. There is insufficient data to know if there is an increased risk of cerebrovascular events associated with NOZINAN. An increased risk with other antipsychotic drugs or with other populations of patients cannot be excluded.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects with different phenothiazines vary in type, frequency, and mechanism of occurrence, i.e., some are dose-related, while others involve individual patient sensitivity. Some adverse effects may be more likely to occur, or occur with greater intensity, in patients with special medical problems, e.g., patients with mitral insufficiency or pheochromocytoma have experienced severe hypotension following recommended doses of certain phenothiazines.

Phenothiazines have been observed to exert marked sedative effects and have a definite potential to induce parkinsonian syndrome, cause cholestatic hepatitis with intrahepatic obstructive jaundice and precipitate dermatological reactions.

8.2 Clinical Trial Adverse Reactions

Not all of the following adverse reactions have been reported with every phenothiazine derivative, but they have been reported with one or more, and should be borne in mind when drugs of this class are administered.

Adverse reactions may be classified as follows:

Autonomic Nervous System: Dryness of the mouth and, in older patients, occasional urinary retention and tachycardia. Patients should be advised of the risk of severe constipation during NOZINAN treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

Blood: Rare instances of agranulocytosis have been reported. Cases of neutropenia and granulocytopenia have also been reported.

Cardiovascular: Orthostatic hypotension may be encountered at the start of treatment by the parenteral route. Rare cardiac rhythm disturbances, including tachycardia or fibrillation have occurred. Very rare cases of QT interval prolongation have been reported. There have been isolated reports of sudden death, with possible causes of cardiac origin (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 9.4 Drug-Drug Interactions), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Central Nervous System: Drowsiness may appear early in treatment but will gradually disappear during the first weeks or with an adjustment in the dosage. Cases of confusional states, delirium, and seizures have been reported. Phenothiazines, such as NOZINAN, may impair sensitivity and adaptation to changes of environmental temperature, so that fatal hyperthermia and heat strokes are possible complications.

Extrapyramidal effects, including dystonias, akathisia, and parkinsonism, have been reported with antipsychotic medication. These reactions may be corrected either by reducing the dose of NOZINAN or by administering an anticholinergic agent (see 7 WARNINGS AND PRECAUTIONS, 9 DRUG INTERACTIONS).

As with other antipsychotic agents, tardive dyskinesia may occur in patients on long-term therapy and symptoms may persist long after therapy is discontinued or may be permanent, in some cases. The risk appears to be greater in children (including dystonias) and elderly patients. If the signs and symptoms of tardive dyskinesia appear during treatment, dosage reduction or discontinuation of NOZINAN should be considered. Anticholinergic antiparkinsonian agents have no effect and may cause exacerbation (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions).

Endocrine: Weight gain has been occasionally reported in patients during prolonged treatment with high doses. Hyperglycemia or glucose tolerance impaired has been reported in patients treated with NOZINAN (see 7 WARNINGS AND PRECAUTIONS). Altered libido, menstrual irregularities, lactation, false positive pregnancy tests, inhibition of ejaculation, gynecomastia.

Gastrointestinal: Necrotizing colitis, which can be fatal, has been very rarely reported in patients treated with NOZINAN. Chronic constipation, including paralytic ileus.

Hepatobiliary: Rare cases of cholestatic jaundice and liver injury have been observed.

Metabolism and Nutrition: Hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Skin: Skin reaction, rash photosensitivity reactions, pigmentation disorder are extremely rare.

Urogenital: Priapism has been very rarely reported.

Vascular: Cases of venous thromboembolism, including cases of pulmonary embolism, sometimes fatal, and cases of deep vein thrombosis have been reported with antipsychotic drugs (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hematologic).

8.5 Post-Market Adverse Reactions

Blood and lymphatic system disorders:

Leukopenia, eosinophilia, thrombocytopenia (including thrombocytopenic purpura).

Cardiac disorders:

- There have been reports of sudden death, with possible causes of cardiac origin (see 7 WARNINGS AND PRECAUTIONS), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.
- Torsades de pointes
- 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, atrioventricular block, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest have been reported during neuroleptic phenothiazine therapy, possibly related to dosage.

Endocrine disorders:

- temperature regulation disorder, hyperprolactinemia which may result is galactorrhea, gynecomastia, amenorrhea, erectile dysfunction.

Eye disorders:

- accommodation disorder, corneal deposits (brownish deposits in the anterior segment of the eye caused by accumulation of the drug and generally without effect on vision).

Immune System Disorders:

- hypersensitivity, urticaria, angioedema

Investigations:

- Positive serology for antinuclear antibodies without clinical lupus erythematosus
- Liver function test abnormal

Nervous system disorders:

- parkinsonism
- dizziness, insomnia
- dystonia (spasmodic torticollis, oculogyric crises, trismus, etc.)
- Tardive dyskinesia occurring with 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 7 WARNINGS AND PRECAUTIONS)
- Anticholinergic effects such as ileus paralytic, risk of accommodation disorders

Pregnancy, puerperium and perinatal conditions:

- Drug withdrawal syndrome neonatal (see 7 WARNINGS AND PRECAUTIONS)

Psychiatric disorders:

- Indifference, anxiety, mood altered

Renal and urinary disorders:

- risk of urinary retention

Respiratory, thoracic and mediastinal disorders:

- respiratory depression, nasal congestion

Reproductive System and Breast Disorders:

- ejaculation disorder

Vascular disorders:

- orthostatic hypotension

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interaction
NOZINAN should not be used with dopaminergics, due to mutual antagonism between dopaminergics and neuroleptics. See 2 CONTRAINDICATIONS and detailed information in 9.4 Drug-Drug Interactions.

9.2 Drug Interactions Overview

NOZINAN potentiates the action of other phenothiazines and CNS depressants (barbiturates, analgesics, narcotics and antihistaminics). The usual doses of these agents should be reduced by half if they are to be given concomitantly with NOZINAN until the dosage of the latter has been established.

9.3 Drug-Behavioural Interactions

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.

9.4 Drug-Drug Interactions

Contraindicated combinations:
NOZINAN should not be used with dopaminergics, due to mutual antagonism between dopaminergics and neuroleptics. Where treatment for neuroleptic-induced extrapyramidal symptoms is required, anticholinergic antiparkinsonian agents should be used in preference to levodopa, since neuroleptics antagonize the antiparkinsonian action of dopaminergics.

Dopaminergics may cause or exacerbate psychotic disorders. If treatment with neuroleptics is required in patients with Parkinson's disease treated with a dopaminergic, the latter should be tapered off gradually, as sudden discontinuation of dopaminergic agents exposes the patient to a risk of NMS. For parkinsonian patients who require treatment with both a neuroleptic and a dopaminergic agent, use the minimum effective doses of both medications.

The action of some drugs may be opposed by phenothiazine neuroleptics; these include amphetamine, clonidine, and adrenaline.

Combinations not recommended or requiring precaution:
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.

Neuroleptic phenothiazines may potentiate QT interval prolongation. QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalemia, and congenital or acquired (i.e., drug induced) QT prolongation (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Methotrimeprazine is a moderate inhibitor of CYP2D6. There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines, and CYP2D6 substrates. Co-administration of methotrimeprazine with amitriptyline/amitriptylinoxide, a CYP2D6 substrate, may lead to an increase in the plasma levels of amitriptyline/amitriptylinoxide. Monitor patients for dose-dependent adverse reactions associated with amitriptyline/amitriptylinoxide.

NOZINAN should be avoided in patients taking monamine oxidase inhibitors within the previous 14 days, and monamine oxidase inhibitors should be avoided while using NOZINAN.

Because of convulsive risk, the combined use of medicinal products which lower the seizure threshold should be carefully assessed.

Gastro-intestinal agents that are not absorbed (magnesium, aluminium and calcium salts, oxides and hydroxides): Reduced gastro-intestinal absorption of phenothiazine neuroleptics may occur. Such gastro-intestinal agents should not be taken at the same time as phenothiazine neuroleptics (at least 2 hours apart, if possible).

Administration of NOZINAN in patients taking antidiabetic agents can lead to an increase in blood sugar levels. Forewarn the patient and advise increased self-monitoring of blood and urine levels.

If necessary, adjust the antidiabetic dosage during and after discontinuing neuroleptic treatment.

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

Guanethidine: Inhibition of the antihypertensive effect of guanethidine.

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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

False positive or negative pregnancy tests have occurred in patients receiving phenothiazine therapy.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

NOZINAN possesses antipsychotic, tranquilizing, anxiolytic, sedative and analgesic properties.

NOZINAN possesses strong sedative properties. It potentiates the pharmacological actions of anesthetics and opioids. It also exerts a potent anti-apomorphine effect, a hypothermic action 3 times more potent than that of chlorpromazine and strong antispasmodic and anti-histaminic effects.

NOZINAN is capable of reversing epinephrine-induced hypertension but has practically no effect against norepinephrine and acetylcholine. It readily protects rats against traumatic shock.

10.2 Pharmacodynamics

Information is not available.

10.3 Pharmacokinetics

Information is not available.

11 STORAGE, STABILITY AND DISPOSAL

NOZINAN (methotrimeprazine hydrochloride) injectable should be stored at 15°C to 30°C. Protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

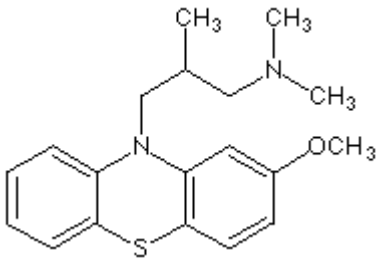
Drug Substance

Proper name: Methotrimeprazine hydrochloride

Chemical name: 2-methoxy-N,N,β-trimethyl-10H-phenothiazine-10-propamine hydrochloride

Molecular formula and molecular mass: $C_{19}H_{24}N_2OS \bullet HCl$ and 364.9

Structural formula:



• HCl

Physicochemical properties: White to very slightly yellow, slightly hygroscopic powder

Product Characteristics:

Solubility: Freely soluble in water and in alcohol, practically insoluble in ether

Melting point: 142˚C and 162˚C

14 CLINICAL TRIALS

Data on which indications were initially approved is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In mice the LD_{50} of NOZINAN is 70 mg/kg i.v., 250 mg/kg s.c., 344 mg/kg i.p. and 380 mg/kg p.o. Signs of acute toxicity consist of CNS depression interrupted by periods of convulsions and uncoordinated movements.

In the rat, a daily dose of 5 or 10 mg/kg p.o. for 4 consecutive weeks did not produce any digestive issues or weight loss. During the first days of treatment, a state of depression appeared, which was most pronounced on the third or fourth day and then almost completely disappeared. Laboratory and function tests indicated no renal, hepatic or blood anomalies. Microscopic visceral examinations revealed no toxic lesions.

In the dog, a daily dose of 2.5 or 5 mg/kg p.o. for 4 consecutive weeks did not affect weight stability but animals appeared lethargic. Some relaxation of the nictitating membrane and a transient reduction of blood pressure were observed. During treatment, the leucocyte count and blood coagulation remained normal. Anatomopathological examination of the visceral parenchyma of sacrificed animals confirmed that all organs remained normal.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrNOZINAN®

Methotrimeprazine Hydrochloride Injection, USP

Read this carefully before you start taking **NOZINAN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NOZINAN**.

Serious Warnings and Precautions
Drugs like NOZINAN can raise the risk of death in elderly people who have dementia. NOZINAN is not to be used in patients with dementia.

What is NOZINAN used for?

NOZINAN is used to:

- treat mental health problems that cause abnormal thinking and perception including schizophrenia, psychosis in the elderly and manic depressive syndromes
- control pain from various causes such as cancer, shingles, pain in the nerves of the face or ribs, and muscle pain
- treat nausea and vomiting
- manage insomnia

How does NOZINAN work?

Exactly how NOZINAN works is unknown, however it possesses properties that:

- reduce and control psychotic symptoms,
- tranquilize,
- reduce anxiety,
- induce sleep,
- relieve pain.

What are the ingredients in NOZINAN?

Medicinal ingredients: methotrimeprazine (as hydrochloride)

Non-medicinal ingredients: ascorbic acid, sodium chloride, sodium sulfite and water for injection.

NOZINAN comes in the following dosage forms:

Solution for injection: 25 mg/mL

Do not use NOZINAN if:

- you/your child are allergic to methotrimeprazine**,** phenothiazines (a type of antipsychotic) or to any of the other ingredients in NOZINAN
- you/your child are taking other drugs used to treat physcotic disorders including dopaminergics

- you/your child are in an altered state of consciousness or coma, due to alcohol, drugs that make you sleepy (hypnotic drugs), or pain medications
- you/your child have liver problems
- you/your child have a blood disorder
- you/your child have a condition called bone marrow depression
- you/your child have a medical condition known as pheochromocytoma (a tumor of the adrenal gland)
- you/your child have a severe heart or blood vessel disorder
- you/your child have severely low blood pressure
- you/your child have brain damage
- you/your child are going to receive anesthesia in the spine or for a large area of the body (such as an arm, leg or the lower part of your body)
- you/your child have a medical condition called myasthenia gravis (muscle weakness and fatigue)
- you/your child have urethra or prostate problems that may impact your/their ability to completely empty your/their bladder (urinary retention)
- you/your child are at risk for having glaucoma (increased pressure in the eye)

NOZINAN is not for use in children less than 1 year of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you/ your child take NOZINAN. Talk about any health conditions or problems you may have, including if you/your child:

- have a heart or blood vessel disease
- have a history of having strokes
- are at risk for developing blood clots or having a stroke. Risk factors include:
    - a family history of blood clots or strokes
    - having diabetes
    - having high cholesterol
    - being over the age of 65
    - smoking
    - being overweight
    - taking oral birth control
    - not being able to move due to air travel or other reasons
- suffer from an enlarged prostate (Benign Prostatic Hyperplasia)
- have or have had seizure disorders (epilepsy)
- have kidney problems
- have Parkinson's disease
- have hypothyroidism (underactive thyroid gland)
- have heart failure (heart does not pump blood as well as it should)
- plan to have surgery
- are pregnant, are planning to become pregnant, or are of child-bearing potential and are not using effective contraception
- are breast-feeding or are planning to breastfeed. NOZINAN passes into the breastmilk. You should not breastfeed if you are taking NOZINAN
- are 65 years of age or older
- have heart problems or problems with your heart beat

- have low levels of potassium in the blood
- are taking any medications that affect how your heart beats

Other warnings you should know about:

Do NOT stop taking NOZINAN without talking to your healthcare professional first, as it may cause unwanted side effects such as headache, insomnia, numbness, tingling, burning, or prickling, nervousness, anxiety, nausea, sweating, dizziness, jitteriness and weakness.

Driving and Using Machines: Until you know how NOZINAN affects you, do not drive or use machinery, especially when you first start treatment. Taking NOZINAN can cause side effects such as:

- drowsiness
- dizziness, and
- blurred vision.

Effects on Newborns: In some cases, babies born to a mother taking NOZINAN during pregnancy have symptoms that are severe that require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. You should be ready to get emergency medical help for your newborn if they:

- have trouble breathing
- are overly sleepy
- have muscle stiffness or floppy muscles (like a ragdoll)
- are shaking or
- have difficulty feeding

Increased levels of prolactin: NOZINAN can raise the levels or a hormone called “prolactin”. If you have high levels of prolactin and a condition called hypogonadism, you may be at an increased risk of breaking a bone due to osteoporosis. This occurs in both men and women. High levels of prolactin may also impair fertility in both men and women.

Dehydration and Overheating: It is important to not become too hot or dehydrated while you are taking NOZINAN.

- Do not exercise too much
- In hot weather, stay inside in a cool place is possible
- Stay out of the sun
- Do not wear too much clothing or heavy clothing
- Drink plenty of water

Monitoring and laboratory tests: Your healthcare professional should do tests before starting treatment with NOZINAN and while you are taking it. These tests will monitor:

- blood sugar,
- body weight,
- blood count,
- liver and kidney,
- blood pressure, and
- if you/your child develop a sore throat, fever and weakness

Sensitivity to sunlight: NOZINAN may increase sensitivity to sunlight. You/your child should wear sunscreen if you/they will be spending time outside.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interaction
NOZINAN should not be used if you are taking dopaminergics which are used to treat Parkinson's disease.

The following may interact with NOZINAN:

- alcohol. You should avoid drinking alcohol while on NOZINAN.
- drugs used to treat mental and emotional disorders called phenothiazines
- drugs used to treat allergies
- drugs used to treat insomnia, anxiety, panic attacks and seizures
- drugs used to relieve pain such as narcotics, analgesics and amitriptylinoxide
- drugs used manage psychosis
- drugs used to treat heart rhythm problems such as atropine
- drugs that cause electrolyte imbalance such as water pills, amphotericin B, corticosteroids and laxatives
- drugs used to treat depression such as monoamine oxidase inhibitors and amitriptyline
- drugs that lower the seizure threshold
- drugs used to treat gastrointestinal disorders such as magnesium, aluminum and calcium salts, oxides and hydroxides
- drugs used to treat diabetes
- drugs used lower blood pressure, such as guanethidine
- drug used to treat mental health problems called lithium

NOZINAN may cause a false reading of some types of pregnancy tests. For more information, talk to your healthcare professional.

How to take NOZINAN:

- NOZINAN will be given to you/your child by a healthcare professional.
- For adults, the solution of NOZINAN will be given 3 or 4 times a day through a needle placed in a large muscle. This is called intramuscular (IM) injection.
- For children, the solution of NOZINAN is given 1 or more times a day as an IM injection or as an infusion into the vein. This is called intravenous infusion.
- After you/your child have been given NOZINAN, you/your child should remain lying down for at least one hour.

Usual dose:

The usual dose of NOZINAN will be different for everyone. Your/your child's healthcare professional will decide on the dose that is right for you/your child. Your/your child's dose will depend on age, weight and other conditions or illnesses you/your child have.

Overdose:

The signs of an overdose may include drowsiness, spasm, shaking, seizure, low blood pressure, difficulty breathing and coma.

If you think you, or a person you are caring for, have taken too much NOZINAN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you/your child miss a dose, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take 2 doses at once.

What are possible side effects from using NOZINAN?

These are not all the possible side effects you may have when taking NOZINAN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects include:

- drowsiness
- dryness of the mouth
- constipation and difficulty urinating
- weight gain
- skin may be more sensitive to sunlight

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	
UNCOMMON			
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			√
Oropharyngeal disorder: soreness of the mouth, gums or throat.			√
Heart rhythm problems: dizziness, light headedness, shortness of			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
breath, racing heart, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures			
Extrapyramidal reactions: tremor, muscle stiffness, body spasm, impairment of voluntary movement, upward eye rolling, exaggeration of reflexes or drooling			√
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		√	
Respiratory Depression (also known as hypoventilation): slow, shallow or weak breathing; blue lips, fingers, toes; confusion; headaches			√
Seizures (fit)**:** uncontrollable shaking with or without loss of consciousness		√	
Tardive Dyskinesia: muscle twitching or unusual/abnormal movement of the face or tongue or other parts of your body			√
Thromboembolism (blood clot in a vein or artery): pain or tenderness or swelling in your arm or leg, skin that is red or warm, coldness, tingling or numbness, pale skin, muscle pain or spasms, weakness			√
Priapism: long-lasting (greater than 4 hours in duration) and painful erection of the penis			√
New or worsening constipation		√	
Liver Injury: pain in the right abdomen, fever, fatigue, weakness, nausea, vomiting, loss of appetite, yellowing of the skin or eyes, dark urine		√	
UNKNOWN			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Paralytic Ileus: abdominal pain or discomfort and constipation, due to inactive intestinal muscles		√	
Reduced vision		√	
Behavior and mood changes: indifference, anxiety, anger		√	
Dystonia: twisting movements that you cannot control and can affect posture or the face including eyes, mouth, tongue or jaw, tightness of the throat, difficulty swallowing or breathing which may lead to choking			√
Akathisia: restlessness, inability to stay still, fidgeting, pacing			√
Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		√	
Neuroleptic Malignant Syndrome: pronounced muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness			√
Agranulocytosis (decrease in white blood cells): frequent infection with fever, chills, sore throat			√
Neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms			√
Hyperprolactinemia (elevated prolactin levels): irregular menstrual cycles, production and discharge of breast milk, abnormal hair growth, infertility			√
Feeling very hot and unable to cool down (generally as a result of several factor together, such as vigorous exercise, dehydration, warm conditions)		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Necrotising colitis: (serious disease that affects the intestines): swelling or bloating in the abdomen, discolouration of the abdomen, bloody stool, diarrhea, vomiting			√
SIADH—syndrome of inappropriate antidiuretic hormone secretion: concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (antidiuretic hormone).			√
Torsade de pointes (life-threatening irregular heartbeat)			√
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness			√
Eosinophilia (increased numbers of certain white blood cells): abdominal pain, rash, weight loss, wheezing.		√	
Hyperthermia (very high body temperature): severe muscle spasms, fast heart rate		√	
Gynecomastia: breast enlargement in men (and /or women)			√
Vaginal bleeding changes: increased or decreased menstrual bleeding, spotting, infrequent periods or absence of bleeding			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store NOZINAN at room temperature (15˚C to 30˚C). Protect from light.

Keep out of reach and sight of children.

If you want more information about NOZINAN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the importer's website www.xediton.com, or by calling 1-888-XEDITON (933-4866).

This leaflet was prepared by neuraxpharm Arzneimittel GmbH.

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