

**PRODUCT MONOGRAPH**  
**INCLUDING CONSUMER INFORMATION**

**PrNOZINAN<sup>®</sup>**

**Methotrimeprazine Hydrochloride Injection, USP**  
**25 mg/mL methotrimeprazine as methotrimeprazine hydrochloride**

**Neuroleptic**

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## **PRODUCT MONOGRAPH**

<sup>Pr</sup>NOZINAN<sup>®</sup>

Methotrimeprazine Hydrochloride Injection, USP

### **THERAPEUTIC CLASSIFICATION**

Neuroleptic

### **ACTION AND CLINICAL PHARMACOLOGY**

Nozinan<sup>®</sup> possesses antipsychotic, tranquilizing, anxiolytic, sedative and analgesic properties.

### **INDICATIONS AND CLINICAL USE**

Nozinan (methotrimeprazine hydrochloride injection) is indicated for:

- Psychotic disturbances: acute and chronic schizophrenias, senile psychoses, manic-depressive syndromes.

Nozinan may also be useful as:

- an analgesic: In pain due to cancer, zona, trigeminal neuralgia, neurocostal neuralgia, in phantom limb pains, muscular discomforts and as post-operative analgesic adjunct.
- an antiemetic: For the treatment of nausea and vomiting of central origin.
- a sedative: For the management of insomnia.

### **CONTRAINDICATIONS**

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

- hypersensitivity to methotrimeprazine or to any ingredient in the formulation or component of the container;
- sensitivity to phenothiazines;
- coma or CNS depression due to alcohol, hypnotics, analgesics or narcotics;
- blood dyscrasia;

- hepatic impairment;
- brain damage;
- pheochromocytoma;
- circulatory collapse/severe hypotension, or severe heart disorder;
- regional or spinal anesthesia;
- risk of urinary retention related to urethroprostatic disorders;
- risk of closed angle glaucoma;
- history of agranulocytosis;
- concomitant use of dopaminergics.

## **WARNINGS**

### General:

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

### Parkinson's Disease:

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

### Elderly Patients with Dementia:

Nozinan is not indicated for the treatment of patients with dementia. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in elderly patients with dementia showed a mean 1.6 fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear (see PRECAUTIONS, Mortality in Geriatric Patients with Dementia-related Psychosis, and Cerebrovascular Adverse Events (CVAEs) including stroke in Elderly Patients with Dementia).

### Occupational Hazards:

Nozinan can reduce psychomotor activity especially during the first few days of treatment. Patients should therefore be cautioned not to drive a motor vehicle or to participate in activities requiring total mental alertness.

### 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.

Cardiovascular system:

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 also PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS).

Tardive Dyskinesia:

The risk of onset of tardive dyskinesia, even at low doses, particularly in children and the elderly, should be taken into account. As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstated, when the dosage is increased or when a switch is made to a different antipsychotic drug. 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.

Neuroleptic Malignant Syndrome:

Neuroleptic malignant syndrome (NMS) may occur in patients receiving antipsychotic drugs. If unexplained fever occurs, treatment should be discontinued since this may be one of the symptoms of the NMS reported with neuroleptic drugs. NMS is characterized by pallor, hyperthermia, muscle rigidity, altered consciousness, and signs of autonomic instability including irregular blood pressure, tachycardia, cardiac arrhythmias and diaphoresis. Additional signs may include elevated serum creatine kinase, myoglobinuria (rhabdomyolysis), acute renal failure and leukocytosis. Signs of autonomic dysfunction, such as sweating and irregular pulse or blood pressure, may precede the onset of hyperthermia and thus constitute early warning signs of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted. Although this effect of neuroleptics may be idiosyncratic in origin, there may be predisposing risk factors, such as dehydration and organic brain damage.

Immune system:

All patients should be advised that, if they experience fever, sore throat or any other infection, they should inform their physician immediately and undergo a complete blood count. Treatment should be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the blood count.

Gastrointestinal system:

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

Very rare cases of potentially fatal necrotising enterocolitis have been reported (see ADVERSE REACTIONS).

Reproductive system:

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.

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 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 PRECAUTIONS, Mortality in Geriatric Patients with Dementia-related Psychosis, and Cerebrovascular Adverse Events (CVAEs) including stroke in Elderly Patients with Dementia).

Pregnant Women:

Since the safety of Nozinan during pregnancy has not been established, Nozinan should not be used during pregnancy or in women of child bearing potential unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

*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.

*Lactation:*

Nozinan is excreted in human breast milk in low amounts. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Nozinan therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility disorders:

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.

## **PRECAUTIONS**

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.

Nozinan therapy should be initiated at low doses in patients with arteriosclerosis or cardiovascular problems.

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

During long-term therapy, periodic liver function tests should be performed. In addition, blood counts 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. It is advisable to administer an appropriate anticonvulsant medication to epileptic patients receiving Nozinan therapy.

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
- patients with severe renal impairment, due to the risk of accumulation
- elderly patients exhibiting greater susceptibility to orthostatic hypotension, sedation and extrapyramidal effects; chronic constipation (risk of paralytic ileus); possible prostatic hypertrophy

Patients are strongly advised not to consume alcoholic beverages or to take medicines containing alcohol during treatment.

Patients should remain lying down for at least one hour after injection due to the risk of hypotension.

### Drug Interactions

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.

#### *Contraindicated combinations:*

Nozinan should not be used with dopaminergics, due to mutual antagonism between dopaminergics and neuroleptics. Neuroleptic-induced extrapyramidal syndrome should be treated with an anticholinergic agent rather than dopaminergics.

Dopaminergics may cause or exacerbate psychotic disorders. If treatment with neuroleptics is required in patients with Parkinson's Disease treated with dopaminergics, the latter should be tapered off gradually, as sudden discontinuation of dopaminergic agents exposes the patient to a risk of NMS.

#### *Combinations not recommended:*

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 WARNINGS, Cardiovascular).

*Combinations requiring precaution:*

Cytochrome P450 2D6 (CYP2D6) Metabolism: Phenothiazines, including Nozinan, are substrates and inhibitors of CYP2D6, and pharmacokinetic interactions have been reported between and CYP2D6 substrates and phenothiazines. Nozinan and its non-hydroxylated metabolites are reported to be potent inhibitors of CYP2D6.

Coadministration of Nozinan and a drug primarily metabolized by the CYP2D6 enzyme system may alter the plasma concentration of either drug. Monitor patients for efficacy and potentially serious dose-dependent adverse reactions associated with Nozinan and co-administered CYP2D6 substrates such as codeine, venlafaxine, amitriptyline and nortriptyline.

As phenothiazines, such as Nozinan, may lower seizure threshold, the combined use of medicinal products that are proconvulsant, or lower the seizure threshold, should be carefully weighed up due to the severity of the incurred risk (see PRECAUTIONS).

*Combinations to be taken into consideration:*

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

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

Atropine and atropine-like substances: Cumulative adverse effects related to atropine-like substances such as urinary retention, constipation, dry mouth, etc.

Alcohol: 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.

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

*Drug-Laboratory Interactions*

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

*Mortality in Geriatric Patients with Dementia-related Psychosis*

In elderly patients with dementia-related psychosis, the efficacy and safety of Nozinan has not been studied. Observational studies suggest that elderly patients with dementia-



related psychosis treated with antipsychotic drugs are at an increased risk of death. Nozinan is not indicated for the treatment of patients with dementia-related psychosis.

*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. Nozinan is not indicated in elderly patients with dementia.

*Vascular disease*

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.

*Endocrine and metabolism*

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.

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

*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.

## **ADVERSE REACTIONS**

May be classified as follows:

**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, convulsions and epileptic seizures have been reported.

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 PRECAUTIONS, 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 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 ADVERSE REACTIONS, Post-Market Adverse Reactions).

**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.

**Cardiovascular:** Orthostatic hypotension may be encountered at the start of treatment by the parenteral route. 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 WARNINGS, Cardiovascular and PRECAUTIONS, Drug Interactions), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

**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 WARNINGS, Vascular disorders).

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

**Endocrine:** Weight gain has been occasionally reported in patients during prolonged treatment with high doses. Hyperglycemia or intolerance to glucose has been reported in patients treated with Nozinan (see PRECAUTIONS, Endocrine and metabolism).

**Gastrointestinal:** Necrotizing enterocolitis, which can be fatal, has been very rarely reported in patients treated with Nozinan.

**Hepatobiliary:** Rare cases of cholestatic jaundice without liver damage have been observed. Cases of hepatocellular, cholestatic and mixed liver injury have also been reported.

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

**Skin:** Skin reactions due to photosensitivity or allergies are extremely rare.

**Urogenital:** Priapism has been very rarely reported.

**Post-Market Adverse Reactions:**

Blood and lymphatic system disorders:

- Leukocytopenia

Cardiac disorders:

- 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, a-v block, ventricular tachycardia, which may result in ventricular fibrillation or cardiac arrest have been reported during neuroleptic phenothiazine therapy, possibly related to dosage

Endocrine disorders:

- Thermoregulation disorders
- Hyperprolactinemia which may result is galactorrhea, gynecomastia, amenorrhea, impotence, frigidity

Eye disorders:

- Brownish deposits in the anterior segment of the eye caused by accumulation of the drug and generally without effect on vision.

Investigations:

- Positive serology for antinuclear antibodies without clinical lupus erythematosus

Nervous system disorders:

- Parkinsonism (with prolonged high dose)
- Early dyskinesia (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 PRECAUTIONS)
- Anticholinergic effects such as paralytic ileus, risk of accommodation disorders

Pregnancy, puerperium and perinatal conditions:

- Drug withdrawal syndrome neonatal (see WARNINGS)

Psychiatric disorders:

- Indifference, anxiety reactions, mood changes

## **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

*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.

## **DOSAGE AND ADMINISTRATION**

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

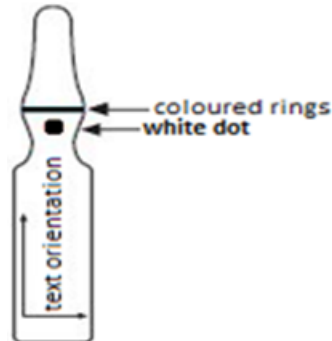
I.M.: A total daily dose of 0.0625 to 0.125 mg/kg, given once daily or in divided doses. Oral medication should be substituted as soon as possible.

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).

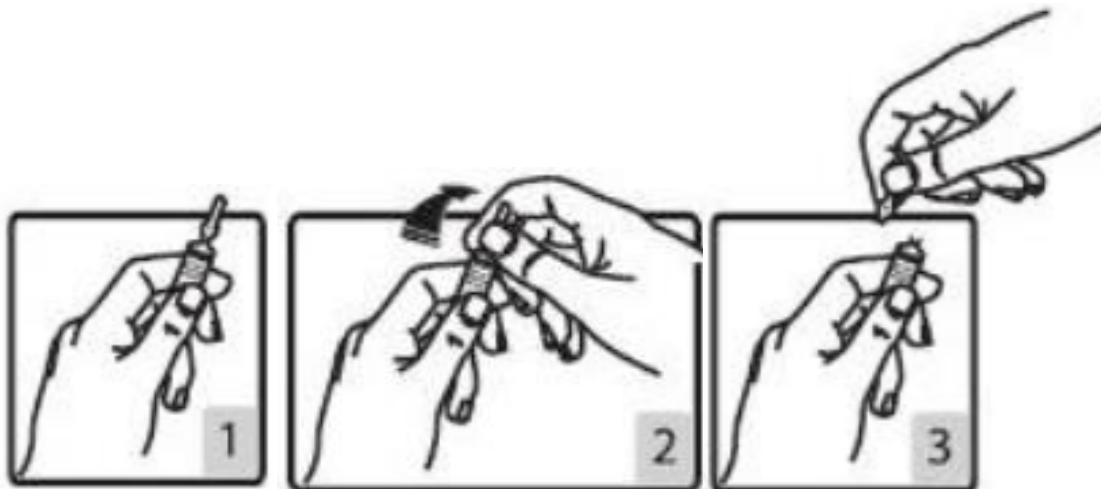
## SPECIAL HANDLING INSTRUCTIONS

### 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.



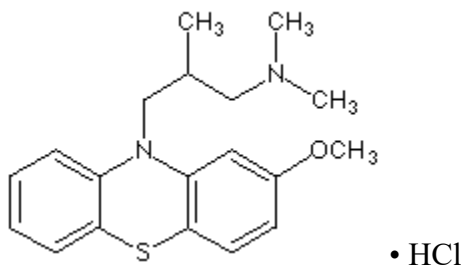
- Hold the bottom part of the ampoule upright with one hand. If there is liquid in the top or stem of the ampoule, gently tap the top to move it to the bottom of the ampoule.
- Position the ampoule as indicated in Picture 1, with your thumb at or below the stem, pointing towards the white dot. Do not 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.



## PHARMACEUTICAL INFORMATION

### Drug substance

Proper name: Methotrimeprazine hydrochloride  
Chemical name: 2-methoxy-N,N,β-trimethyl-10H-phenothiazine-10-propamine hydrochloride  
Structural formula:



Molecular formula:  $C_{19}H_{24}N_2OS \cdot HCl$   
Molecular weight: 364.9  
Physical form: White to very slightly yellow, slightly hygroscopic powder  
Solubility: Freely soluble in water and in alcohol, practically insoluble in ether  
Melting point: 142°C and 162°C

### Composition

Each mL contains: methotrimeprazine base 25 mg (as the hydrochloride). Non-medicinal ingredients: 0.1% ascorbic acid, 0.65% sodium chloride, 0.05% sodium sulfite and water for injection.

## STABILITY AND STORAGE RECOMMENDATION

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

## AVAILABILITY OF DOSAGE FORMS

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

Nozinan contains the following nonmedicinal ingredients: 0.1% ascorbic acid, 0.65% sodium chloride, 0.05% sodium sulfite and water for injection.

### **PHARMACOLOGY**

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.

### **TOXICOLOGY**

In mice the LD<sub>50</sub> 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 troubles 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 remain normal.



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## IMPORTANT: PLEASE READ

### CONSUMER INFORMATION

PrNOZINAN®

#### Methotrimeprazine Hydrochloride Injection, USP

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Nozinan®. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

Nozinan is used to treat psychotic disturbances, such as acute and chronic schizophrenia, psychosis in the elderly, and manic-depressive syndromes.

Nozinan may also be used to control pain due to various causes, to control nausea and vomiting or for the management of insomnia.

Ask your doctor if you have any questions about why Nozinan has been prescribed to you.

##### What it does:

Nozinan helps to:

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

##### When it should not be used:

Do not use Nozinan if you:

- are allergic to Nozinan, to phenothiazines (a type of antipsychotic) or to any of the ingredients in the product
- are in an altered state of consciousness or coma, due to alcohol, hypnotic drugs, or pain medications
- have liver disease
- have a blood disorder
- have a medical condition known as pheochromocytoma (a tumor of the adrenal gland)
- have a severe heart or blood vessel disorder
- have severely low blood pressure
- had brain damage
- have drowsiness, slow breathing, weak pulse
- Are going to receive anesthesia in the spine or for a region (such as an arm, leg or the lower part of your body)
- are at risk for urinary retention due to disorders of the urethra or prostate;
- are at risk of having glaucoma (increased pressure in the eye);

- have a history of agranulocytosis (low level of neutrocytes in your blood);
  - are taking medicines known as dopaminergics
- Nozinan is not indicated in elderly patients with dementia (mental decline) and is not recommended for use in patients with Parkinson's Disease.

##### What the medicinal ingredient is:

Methotrimeprazine hydrochloride.

##### What the nonmedicinal ingredients are:

0.1% ascorbic acid, 0.65% sodium chloride, 0.05% sodium sulfite and water for injection.

##### What dosage forms it comes in:

Solution for injection: 25 mg/mL

#### WARNINGS AND PRECAUTIONS

During the first few days of treatment, Nozinan may cause some people to become drowsy or less alert. You should not drive a car, operate machinery or participate in activities requiring alertness until you know how Nozinan affects you.

Muscular, neurologic, vascular, cardiac disorders, and hyperglycemia may occur in some patients taking Nozinan.

Nozinan is not recommended in pregnancy. In some cases, babies born to a mother taking Nozinan during pregnancy have experienced symptoms that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be prepared to seek immediate emergency medical attention for your newborn if they have difficulty breathing, are overly sleepy, have muscle stiffness, or floppy muscles (like a rag doll), are shaking, or are having difficulty feeding. Some babies born to mothers who are taking antipsychotic medicines have birth defects. It is important to talk to your doctor about the risks and benefits of taking Nozinan during pregnancy.

Effects on fertility: Nozinan may affect the fertility in both men and women.

##### **Before using Nozinan, tell your doctor or pharmacist if you:**

- have heart or blood vessel disease
- have a history of cerebrovascular disease including strokes or transient ischemic attacks (mini-strokes)
- suffer from an enlarged prostate (Benign Prostatic Hyperplasia)
- have or have had seizure disorders (e.g. epilepsy)
- have severe kidney problems
- have Parkinson's Disease
- have hypothyroidism (underactive thyroid gland)
- have cardiac failure (reduced functioning of heart muscles)

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- have myasthenia gravis (a disease that causes weakness in your muscles)
- plan to have surgery (or a procedure requiring anesthetics)
- are pregnant, are planning to become pregnant, or are of child-bearing potential and are not using effective contraception
- are breast-feeding

If you are given Nozinan and think that you may be exposed to extreme heat, or if you perform activities which may increase your body temperature (for example exercising vigorously or working in hot, sunny places) or if you are dehydrated, consult your doctor. Nozinan can affect the body's ability to regulate temperature.

If you experience severe constipation and you are elderly, please consult your doctor as soon as possible.

During long-term therapy, periodic liver function tests should be done.

### INTERACTIONS WITH THIS MEDICATION

The combination of Nozinan with some medicines can increase the quantity of other medicines in your body. This can lead to an increase in the risk of having side effects. Before using any prescription, over-the-counter medicines or herbal products, check with your doctor or your pharmacist.

#### Drugs that may interact with Nozinan include:

- Nozinan should not be used with drugs known as dopaminergics. If you are taking dopaminergics to treat your Parkinson's Disease, your doctor may slowly stop your treatment with dopaminergics before starting treatment with Nozinan.
- Nozinan is not recommended to be used with the following drugs:
  - drugs that prolong the QT interval (including certain antiarrhythmics, antidepressants and other antipsychotics)
  - drugs that cause electrolyte imbalance (including water pills, amphotericin B, corticosteroids and laxatives)
- Nozinan should be used with caution with the following drugs:
  - drug metabolized by the CYP2D6 enzyme system (including codeine, venlafaxine, amitriptyline and nortriptyline)
  - drugs that lower the seizure threshold, or lower blood pressure
  - guanethidine
  - atropine and atropine-like substances
  - lithium
- Nozinan may intensify the side effects (such as drowsiness) of the following drugs:

- allergy pills
- sleeping pills
- pain killers
- medications for seizure
- anti-depressant pills
- medications for mental illness

#### Drug - Lifestyle Interactions:

- Nozinan can add to the effects of alcohol. You should avoid consuming alcoholic beverages while on Nozinan therapy

Nozinan may cause a false reading of some types of pregnancy tests. For further information, please consult your doctor or your pharmacist.

### PROPER USE OF THIS MEDICATION

#### Usual dose:

Your doctor will decide the best dose for you based on your individual situation and needs. It is important to take Nozinan the way your doctor told you. Your doctor may increase or decrease your dose depending on your response.

You should remain lying down for at least one hour after your injection, because you may experience a decrease in blood pressure.

You may experience side effects if the drug is stopped suddenly. Contact your physician before stopping your drug.

#### For Adults

- Nozinan is given as an injection into the muscle. The number of times you receive an injection per day will depend on your condition.

#### For Children: the dose is based on the body weight

- Nozinan may be given as an injection into the muscle.
- Nozinan may also be given as a slow infusion in the vein that is diluted with a glucose solution.

#### Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

The signs that you have taken too much Nozinan may include drowsiness, spasm, shaking, seizure, low blood pressure, difficulty breathing and coma.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Nozinan, like any medication, may cause some side effects. Discuss with your doctor if you do experience side effects.

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Side effects include:

- drowsiness may appear early in treatment but usually disappears during the first weeks. If this effect persists, discuss this with your doctor. Your medication might have to be reduced.
- dryness of the mouth.
- in older patients, constipation and difficulty urinating.

Less common side effects include:

- weight gain has been occasionally reported in patients during long-term treatment with high doses.
- your skin may be more sensitive to sunlight.

Your doctor should check your body weight before starting Nozinan and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting Nozinan.

Your doctor will monitor your blood sugar, and your number of white blood cells. Should symptoms such as sore throat or fever appear, consult your doctor. Your doctor should continue to monitor your blood for as long as you are being treated.

If you have high levels of prolactin (measured with a blood test) and a condition called hypogonadism, you may be at increased risk of breaking a bone due to osteoporosis. This occurs in both men and women.

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency assistance
	Only if severe	In all cases	
<b>Common</b>			
Low blood pressure with symptoms such as feeling dizzy, especially when getting up from a lying or sitting position		√	
<b>Uncommon</b>			
Allergic reactions, such as skin rash, redness or itching			√
Soreness of the mouth, gums or throat, abdominal pain or jaundice			√
Rapid or irregular heart beat, high or low blood pressure			√

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency assistance
	Only if severe	In all cases	
Tremor, muscle stiffness, body spasm, impairment of voluntary movement, upward eye rolling, exaggeration of reflexes or drooling, convulsions and epileptic seizures.			√
Hyperglycemia (too much sugar in the blood) with symptoms such as increased thirst, decreased appetite, nausea or vomiting		√	
Respiratory infection, fever, flu-like symptoms, coughing, difficult or fast breathing			√
Increased sweating, confusion, reduced consciousness			√
Muscle twitching, uncontrolled movements of the mouth, tongue, face or jaw			√
Pain, swelling, redness or warmth in arms or legs, chest pain, anxiety, coughing up blood			√
Long-lasting (greater than 4 hours in duration) and painful erection of the penis			√
New or worsening constipation		√	
Liver disease with symptoms such as abdominal pain, nausea, vomiting, loss of appetite, yellowing of the skin or eyes, dark urine, light-coloured stools.		√	
<b>Unknown</b>			
Abdominal pain or discomfort and constipation, due to inactive intestinal muscles (paralytic ileus)		√	
Reduced vision		√	
Psychiatric disorders, such as indifference, anxiety reactions, or mood changes		√	
Uncontrollable muscle contractions or spasms, causing abnormal fixed postures or twisting and repetitive movements			√
Restlessness, inability to stay still, fidgeting, pacing			√

## IMPORTANT: PLEASE READ

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency assistance
	Only if severe	In all cases	
Hyponatremia (low levels of sodium in your blood) with symptoms such as muscle weakness, spasms or cramps, nausea, vomiting, headache, confusion, fatigue		√	

*This is not a complete list of side effects. For any unexpected effects while taking Nozinan, contact your doctor or pharmacist.*

### HOW TO STORE IT

Nozinan should be stored at room temperature (15°C to 30°C). Protect from exposure to light.

Keep out of reach and sight of children.

#### 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/adverse-reaction-reporting.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.*

### MORE INFORMATION

Your physician, nurse and pharmacist are always your best source of information about your condition and treatment. If you have additional questions or concerns, be sure to ask them.

Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by

visiting the Health Canada website (<https://www.canada.ca/en/health-canada.html>); the manufacturer's website [www.sanofi.ca](http://www.sanofi.ca), or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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