PRODUCT MONOGRAPH

INCLUDING CONSUMER INFORMATION

^{Pr}NOZINAN®

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

Neuroleptic

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Date of Revision:
November 6, 2017

Submission Control No.: 208067

s.a version 12.0 dated November 6, 2017

PRODUCT MONOGRAPH

Pr NOZINAN®

Methotrimeprazine Hydrochloride Injection, USP

THERAPEUTIC CLASSIFICATION

Neuroleptic

ACTION AND CLINICAL PHARMACOLOGY

Nozinan® possesses antipsychotic, tranquilizing, anxiolytic, sedative and analgesic properties.

INDICATIONS AND CLINICAL USE

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

Nozinan may also be useful for:

- 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.
- As an antiemetic: For the treatment of nausea and vomiting of central origin.
- As a sedative: For the management of insomnia.

CONTRAINDICATIONS

- 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;
- in patients with blood dyscrasia;
- hepatic impairment;
- brain damage;
- pheochromocytoma;
- circulatory collapse/severe hypotension, or severe heart disorder;
- regional or spinal anesthesia.

WARNINGS

Elderly Patients with Dementia

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. Nozinan is not indicated for the treatment of patients with dementia (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:

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:

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 reinstituted, 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. NMS is characterized by 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. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

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)

Pregnant Women:

Non-teratogenic effects:
Neonates exposed to antipsychotic drugs including Nozinan during the third trimester of pregnancy are at risk for 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 feeding disorder 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.

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.

Congenital malformations:
Animal studies are insufficient with respect to reproductive toxicity. In humans, the teratogenic risk of Nozinan has not been evaluated. Different prospective epidemiological studies conducted with other phenothiazines have yielded contradictory results regarding teratogenic risk. 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. Nozinan should not be administered to pregnant women, particularly during the first trimester of pregnancy, unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

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 hyperprolactinaemia 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 glaucoma or 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.

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.

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.

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 also WARNINGS, Cardiovascular).

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

An increased risk of cerebrovascular adverse events has been seen in the dementia population in clinical trials 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 however 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.

Endocrine and metabolism

Hyperglycaemia 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:

CNS: 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 are rare and usually appear only after prolonged therapy at high doses. These reactions may be corrected either by reducing the dose of Nozinan or by administering an antiparkinsonian agent.

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 disorder**:** 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. Hyperglycaemia 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 disorders: hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

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

Urogenital System: Priapism has been very rarely reported.

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.

Adults

I.M.: 75 to 100 mg total daily dose, to be divided as a 25 mg injection given 3 or 4 times per day by deep I.M. injection in a large muscle. 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

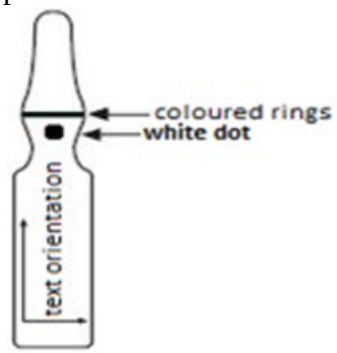
I.M.: A total daily dose of 0.0625 to 0.125 mg/kg, given once daily or in divided doses. Oral medication should be substituted as soon as possible.

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).

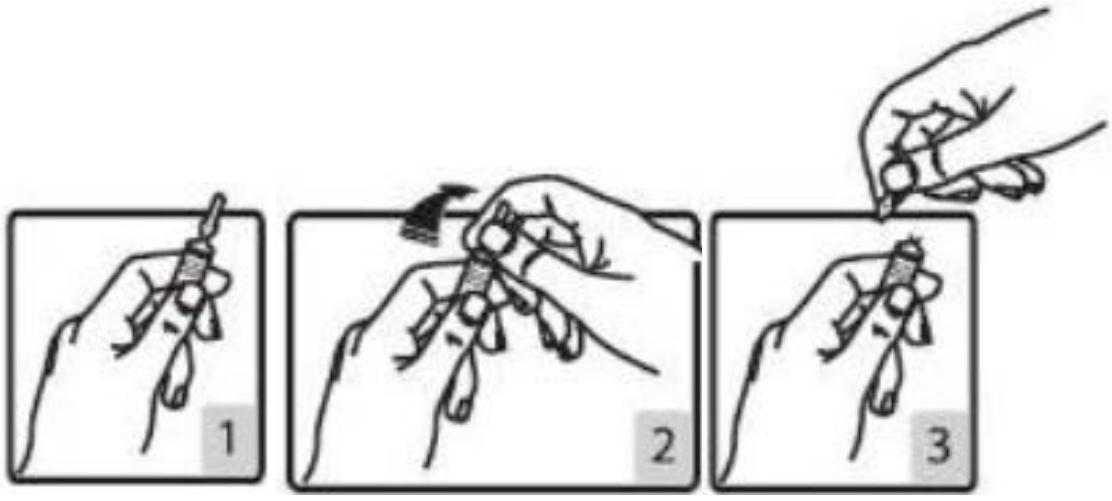
SPECIAL HANDLING INSTRUCTIONS

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.



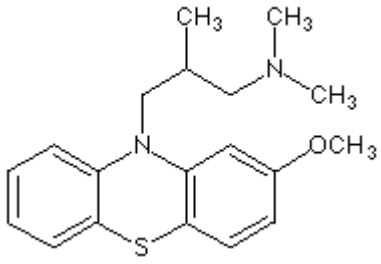
PHARMACEUTICAL INFORMATION

Drug substance

Proper name: Methotrimeprazine hydrochloride

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

Structural formula:



• HCl

Molecular formula: $C_{19}H_{24}N_2OS$ • 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^{o}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_{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 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 completed 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.

REFERENCES

1. Capron M, Lafitte B, Benedit M, Camard CN, Nicolas F, Beligon C, et al. Necrotizing colitis in a 29-year-old man under high-dose neuroleptics. Reanimation Urgences 1999;8(8):701-4.
2. Cubeddu LX. QT prolongation and fatal arrhythmias: a review of clinical implications and effects of drugs. American Journal of Therapeutics 2003;10(6):452-7.
3. Courvoisier S, Ducrot R, Fournel J, Julou L. Propriétés pharmacodynamiques générales de la lévomépromazine (7044 R.P.). C.R. Soc Biologie 1957;151(7):1378-82.
4. Divry P, Boron J, Collard J. La lévomépromazine dans les cures de sommeil potentialisées et les cures neuroleptiques. Acta Neurol Psych Belgica 1959;59(3):325-36.
5. Fekete Z. Control of pruritus with levomepromazine. Appl Therap 1963;5(4):333-4.
6. Fenichel RR, Malik M, Antzelevitch C, Sanguinetti M, Roden DM, Priori SG, et al. Drug-induced torsades de pointes and implications for drug development. J Cardiovasc Electr 2004;15(4):475-95.
7. Filloux MC, Marechal K, Bagheri H, Morales J, Nouvel A, Laurencin G. Phenothiazine-induced acute colitis: A positive rechallenge case report. Clin Neuropharmacol 1999;22(4):244-5.
8. Flamant J. Utilisation à faibles doses d'un nouveau neuroleptique (lévomépromazine, 7044 R.P.) dans le traitement des dystonies neuro-végétatives. L'Hôpital 1960;March H.S.
9. Gram LF, Hansen MG, Sindrup SH, Brösen K, Poulsen JH, Aaes-Jörgensen T, et al. Citalopram: interaction studies with levomepromazine, imipramine and lithium. Ther Drug Monitoring 1993;15:18-24.
10. Hals PA, Dahl SG. Effect of levomepromazine and metabolites on debrisoquine hydroxylation in the rat. Pharmacology & Toxicology 1994;75:255-60.
11. Huot JM, Kristof AC. Lévomépromazine (Nozinan) - a new neuroleptic agent for treatment of senile patients. CMAJ 1959;81:546-8.
12. Kenbubpha K, Silpakit C. Association between antipsychotics and sudden death in psychotic in-patients. International Medical Journal 2002;9(1):27-31.
13. Lambert PA, Beaujard M, Achaintre A, Broussolle P, Perrin J, Berthier C, et al. Essais thérapeutiques d'un nouveau dérivé de la phénothiazine, la lévomépromazine ou 7044 R.P. Ann Medico-Psychol 1957;115(2):291-6.

14. Larrey D, Lainey E, Blanc P, Diaz D, David R, Biaggi A. Acute colitis associated with prolonged administration of neuroleptics. J Clin Gastroenterol 1992;14(1):64-7.

15. Levy L, Ban T. Phenothiazine drugs and the general practitioner. CMAJ 1962;86:415-7.

16. Mehtonen OP, Aranko K, Malkonen L, Vapaatalo H. A survey of sudden death associated with the use of antipsycgotic or antidepressant drugs: 49 cases in Finland. Acta Psychiatr Scand 1991;84:58-64.

17. Muller D. The treatment of restless psychotics with methotrimeprazine (Veractil). J Ment Sci 1961;107(449):783-6.

18. Panaccio V. La lévomépromazine dans le traitement des dermatoses prurigineuses. Union Med Canada 1964;93(3):317-9.

19. Paradis B. La lévomépromazine en anesthésie. Anesthésie-Analgésie 1959;16(1):185-93.

20. Paradis B, Lamontagne A, Gagne-Desrosiers R, Lamarche Y. Association Nozinan-fluothane en anesthésie. Laval Medical 1959;28(3):337-44.

21. Payne P, Veringer D. Levomepromazine in the treatment of neuroleptic resistant psychotics. J Ment Sci 1960;106:1429-31.

22. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiat 2001;58(12):1161-7.

23. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL. Thioridazine and sudden unexplained death in psychiatric in-patients. Brit J Psychiat 2002;180:515-22.

24. Sakurai T, Nishizono M, Nothohara N, Kitahara N. The treatment of schizophrenia with large doses of levomepromazine. Clin Psychiat 1963;4(10):741-54.

25. Sarwer-Foner GJ, Hajnsek F, Groszman M, Grauer H, Koranyi EK. Clinical investigation of levomepromazine (Nozinan) in open psychiatric settings. Med Services J Canada 1961;17(11):798-817.

26. Sigwald J, Bouttier D, Caille F. Le traitement du zona et des algies zostériennes. Étude des résultats obtenus avec la lévomépromazine. Thérapie 1959;14(5):818-24.

27. Sigwald J, Bouttier D, Solignac J. Essai de traitement de la névralgie essentielle du trijumeau par la lévomépromazine. Rev Neurol 1958;99(5):580-1.

28. Sigwald J, Bouttier D, Solignac J, Dumezil. L'action antialgique des phénothiazines. I- Le traitement par la lévomépromazine des algies intenses ou irréductibles. Thérapie 1959;14(6):978-84.

29. Simard-Savoie S, Bloomfield S, Bernier J, Tetreault L. Evaluation clinique des propriétés analgésiques de la lévomépromazine, de la morphine et du placebo sur la douleur chronique. Union Med Canada 1964;93(1):61-7.

30. Syvälathi EKG, Lindberg R, Kallio J, De Vocht M. Inhibitory effects of neuroleptics on debrisoquine oxidation in man. Brit J Clin Pharmacol 1986;22:89-92.

31. Taylor DM. Antipsychotics and QT prolongation. Acta Psychiat Scand 2003;107(2):85-95.

32. Taylor RG, Doku HC. Use of methotrimeprazine after oral surgery. J Dental Med 1967;22:141-3.

33. Zeltser D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S. Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Medicine 2003;82(4):282-90.

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 symptoms of schizophrenias, psychoses, manic-depressive syndromes.

Nozinan may also be used to control pain, 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 (see the section "**What the non-medicinal ingredients are"**)
- Are in an altered state of consciousness or coma, especially if this is caused by alcohol or drug
- 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
- 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)

Nozinan is not indicated in elderly patients with dementia (mental decline).

What the medicinal ingredient is: Methotrimeprazine hydrochloride for injection.

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 are sure Nozinan does not affect you.

Muscular, neurologic, vascular, cardiac disorders, and hyperglycaemia may occur in some patients taking Nozinan (See below the sections **"SIDE EFFECTS AND WHAT TO DO ABOUT THEM"** and **"SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM"**).

Effects on Newborns: 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.

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

Before using Nozinan, tell your doctor if you:
- Have heart or blood vessel disease
- If you have a history of cerebrovascular disease including strokes or transient ischemic attacks (mini-strokes)
- Suffer from an enlarged prostate (Benign Prostatic Hyperplasia)
- Suffer from an increased pressure within the eyes (glaucoma)
- Have or have had seizure disorders (e.g. epilepsy)
- Plan to have surgery (or a procedure requiring anaesthetics)
- Are pregnant or are planning to become pregnant
- Are breast-feeding
- Are taking any other medicines (prescriptions or over the counter medicines)

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IMPORTANT: PLEASE READ

If you are given Nozinan and that you may be exposed to extreme heat or if you perform activities which may increase your body temperature (for example exercising vigorously or work in hot, sunny places) or if you are dehydrated, consult your doctor regarding special cares.

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 the other medicine in your body and therefore the risk of having side effects. Before using any prescription, over-the-counter medicines or herbal products, check with your doctor or your pharmacist.

Drug - drug Interactions: 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 Interaction:

- 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 has decided 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 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.

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 an injection in the vein. The Nozinan injection formulation is to be diluted with a glucose solution and injected slowly into a vein.

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.

If you have taken too much Nozinan, immediately see your doctor, contact your regional Poison Control Centre or go to your nearest hospital emergency department. Do this even if there are no signs of discomfort or poisoning. The signs if you have taken too much Nozinan may include drowsiness, spasm, shaking, seizure, low blood pressure, difficult 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.

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 in 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. They will monitor blood sugar, and the number of infection fighting 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.

IMPORTANT: PLEASE READ

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	
Common			
Low blood pressure (with symptoms such as feeling dizzy, especially when getting up from a lying or sitting position)		√	
Uncommon			
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			√
Tremor, muscle stiffness, body spasm, impairment of voluntary movement, upward eye rolling, exaggeration of reflexes or drooling, convulsions and epileptic seizures.			√
Hyperglycaemia (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.		√	

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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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.

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 Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

Last revised: November 6, 2017