PRODUCT MONOGRAPH

NOZINAN®

Methotrimeprazine Maleate Tablets
5, 25, 50 mg methotrimeprazine as methotrimeprazine maleate

Methotrimeprazine Hydrochloride Injection
25 mg/mL methrorimeprazine as methotrimeprazine hydrochloride

Neuroleptic

sanofi-aventis Canada Inc.
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PRODUCT MONOGRAPH

NAME OF DRUG

NOZINAN®

Methotrimeprazine Maleate Tablets
Methotrimeprazine Hydrochloride Injection

THERAPEUTIC CLASSIFICATION

Neuroleptic

ACTION AND CLINICAL PHARMACOLOGY

Nozinan possesses antipsychotic, tranquilizing, anxiolytic, sedative and analgesic properties and it is also a potent potentiator of anesthetics.

INDICATIONS AND CLINICAL USE

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

Conditions associated with anxiety and tension: autonomic disturbances, personality disturbances, emotional troubles secondary to such physical conditions as resistant pruritus, etc.

Nozinan is also employed:

- As an analgesic: In pain due to cancer, zona, trigeminal neuralgia and neurocostal neuralgia and in phantom limb pains and muscular discomforts.

- As a potentiator of anesthetics: In general anesthesia where it can be used as both a pre- and post-operative sedative and analgesic.

- As an antiemetic: For the treatment of nausea and vomiting of central origin.

- As a sedative: For the management of insomnia.

CONTRAINDICATIONS

In cases of coma or CNS depression due to alcohol, hypnotics, analgesics or narcotics.

It is also contraindicated in patients with blood dyscrasia, hepatic troubles or a sensitivity to phenothiazines.

WARNINGS

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.

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 ADVERSE REACTIONS and DRUG INTERACTIONS).

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.

Elderly patients with dementia treated with certain atypical antipsychotic drugs are at an increased risk of Cerebrovascular Adverse Events (CVAEs) such as stroke and transient ischemic attacks, as well as death, compared to placebo. The mechanism of this increased risk is not known. As an increase in the risk with other antipsychotic drugs cannot be excluded, Nozinan should be used with caution in the elderly with dementia.

Pregnancy: The drug should be used with caution in pregnant women, particularly during the first trimester, unless the benefit to the patient outweighs any possible risk to the fetus.

PRECAUTIONS

In high oral or 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, particularly during the first 2 or 3 months of treatment, and physicians should watch for any signs of blood dyscrasia.

Nozinan does not alter EEG activity. Nevertheless, since phenothiazines can lower the threshold of cortical excitation, 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.

Nozinan and its non-hydroxylated metabolites are reported to be inhibitors of cytochrome P450 2D6. Coadministration of Nozinan and drugs primarily metabolized by the cytochrome P450 2D6 enzyme system may result in increased plasma concentrations of these drugs.

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 AND PRECAUTIONS).

Drug-Laboratory Interactions

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

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.

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, constipation and tachycardia.

Cardiovascular: Orthostatic hypotension may be encountered at the start of treatment by the parenteral route or with high oral doses. 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 and DRUG INTERACTIONS), as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines.

Blood: Rare instances of agranulocytosis have been reported.

Endocrine: Weight gain has been occasionally reported in patients during prolonged treatment with high doses.

Gastrointestinal: Rare cases of cholostatic jaundice without liver damage have been observed. Necrotizing enterocolitis, which can be fatal, has been very rarely reported in patients treated with Nozinan.

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.

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
Oral:
Minor conditions in which Nozinan may be given in low doses as a tranquilizer, anxiolytic, analgesic or sedative: begin treatment with 6 to 25 mg/day in 3 divided doses at mealtimes. Increase the dosage until the optimum level has been reached. As a sedative, a single night time dose of 10 to 25 mg is usually sufficient.

Severe conditions: Such as psychoses or intense pain in which Nozinan is employed at higher doses: Begin treatment with 50 to 75 mg/day divided into 2 or 3 daily doses; increase the dosage until the desired effect is obtained. In certain psychotics, doses may reach 1 g or more/day. If it is necessary to start therapy with higher doses, i.e., 100 to 200 mg/day, administer the drug in divided daily doses and keep the patient in bed for the first few days.

Parenteral:
I.M.: To be used primarily for the initial treatment of psychoses for certain severe pain as a premedication or for the treatment of postoperative pain. In psychoses and pain, doses vary from 75 to 100 mg given as 3 or 4 deep i.m. injections in a large muscle. When given as a premedication or post-operative analgesic, the average dose varies from 10 to 25 mg every 8 hours, which is equivalent to 20 to 40 mg given orally. The last dose during premedication, given 1 hour before surgery, can be 25 to 50 mg i.m.

I.V.: To be used primarily as an infusion during surgery or labour. The dose may range from 10 to 25 mg in 500 mL of a 5% glucose solution administered at a rate of 20 to 40 drops/minute. If Nozinan is administered with a barbiturate or narcotic, the doses of the latter must be reduced by at least one-half.

Children
Oral:
The initial dose has been established at 1/4 mg/kg daily given in 2 or 3 divided doses. This dosage may be increased gradually until an effective level is reached which should not surpass 40 mg/day for a child less than 12 years of age.

Parenteral:
I.M.: A dose of 1/16 to 1/8 mg/kg/day in one or divided among several injections. Oral medication should be substituted as soon as possible.

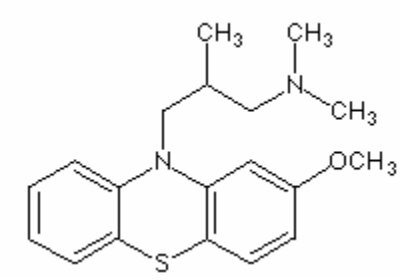
I.V.: In anesthesia, 1/16 mg/kg in 250 mL of a 5% glucose solution may be administered as a slow infusion (20 to 40 drops per minute) during surgery.

PHARMACEUTICAL INFORMATION

Drug substance

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

Structural formula :



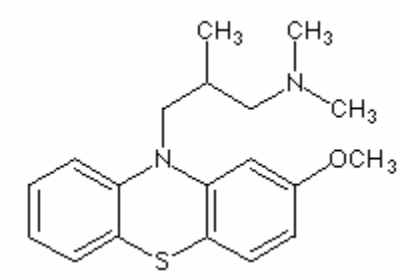
• HCl

Molecular formula :	$C_{19}H_{24}N_2OS \bullet HCl$
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

Drug substance

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

Structural formula :



• $C_4H_4O_4$

Molecular formula :	$C_{19}H_{24}N_2OS \bullet C_4H_4O_4$
Molecular weight :	444.5

Physical form :	White to very slightly yellow crystalline powder
Solubility :	Slightly soluble in water and in alcohol, practically insoluble in ether, sparingly soluble in dichloromethane
Melting point :	186˚C
pH :	3.5 to 5.5

Composition

Injectable: 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.

Tablets: Each yellow tablet contains: methotrimeprazine base 5, 25 or 50 mg (as the maleate). Non-medicinal ingredients: croscarmellose sodium, colloidal silicon dioxide, D&C Yellow #10 Aluminum Lake, dicalcium phosphate, FD&C Yellow #6 Aluminium Lake, magnesium stearate, microcrystalline cellulose, Opadry II White Y-22-7719, polyethylene glycol and talc.

Stability and storage recommendation

Nozinan (methotrimeprazine hydrochloride) injectable and Nozinan (methotrimeprazine maleate) tablets should be stored at 15° 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 (methotrimeprazine base) 5, 25 and 50 mg (as maleate) tablets are available in white HDPE bottles of 100 and 500 tablets.

PHARMACOLOGY

Nozinan possesses strong sedative properties. It potentiates ether and hexobarbital anesthesia as well as morphine analgesia. 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 and produces deep local anesthesia following parasciatic injections.

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.

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CONSUMER INFORMATION

[Pr]NOZINAN®
Methotrimeprazine Maleate Tablets
Methotrimeprazine Hydrochloride Injection

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 or for conditions associated with anxiety and tension.

Nozinan® is also used to control pain, to intensify the effects of anesthetics, 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,
- reduce anxiety,
- induce sleep,
- relieve pain,
- intensify the effects of anesthetics.

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

What the medicinal ingredient is:

Methotrimeprazine maleate for tablets
Methotrimeprazine hydrochloride for injection

What the nonmedicinal ingredients are:
Tablets: Non-medicinal ingredients: croscarmellose sodium, colloidal silicon dioxide, D&C Yellow #10 Aluminum Lake, dicalcium phosphate, FD&C Yellow #6 Aluminium Lake, magnesium stearate, microcrystalline cellulose, Opadry II White Y-22-7719, polyethylene glycol and talc.

Injectable: Non-medicinal ingredients: 0.1% ascorbic acid, 0.65% sodium chloride, 0.05% sodium sulfite and water for injection.

What dosage forms it comes in:

Tablets 5 mg, 25 mg, 50 mg.
Injectable 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.

Tardive dyskinesia, neuroleptic malignant syndrome and cardiac disorders may occur in some patients taking Nozinan® (See the section **"SIDE EFFECTS AND WHAT TO DO ABOUT THEM"**).

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 increase pressure within the eyes (glaucoma)
- Have or have had seizure disorders (e.g. epilepsy)
- Plan to have surgery (or a procedure requiring anaesthetics)
- Are or are planning to become pregnant
- Are breast-feeding

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

Blood counts should also be done regularly, particularly during the first 2 or 3 months of treatment. During long-term therapy, periodic liver function tests should be done.

INTERACTIONS WITH THIS MEDICATION

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

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.

Nozinan® can add to the effects of other drugs that cause drowsiness. Some examples of drugs that cause drowsiness are:

- Drugs for allergies
- Drugs for sleep
- Drugs for pain
- Drugs for seizure
- Drugs for depression
- Drugs for mental illness

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.

Adults

Low doses can be given to tranquilize, reduce anxiety, relieve pain or induce sleep: the initial dose is 6 to 25 mg a day, divided into 3 smaller doses taken with meals. Your doctor may increase your dose if needed. To induce sleep, a single night time dose of 10 to 25 mg is usually sufficient.

Higher doses can be given to reduce symptoms of psychoses or intense pain: the initial dose is 50 to 75 mg a day, divided into 2 or 3 smaller doses. Your doctor may increase your dose if needed.

Injection Dosage Form:

Injection in the muscle: Nozinan® may be given as an injection in the muscle for the initial treatment of psychosis, to control severe pain or before or after a surgery.

Injection in the vein: Nozinan® may be given as an injection in the vein during surgery or labour. The Nozinan® injection formulation is diluted with a glucose solution and injected slowly in a vein.

Children

The dose is based on the body weight. The dose should not exceed 40 mg a day for a child less than 12 years of age.

Injection Dosage Form:

Injection in the muscle: Nozinan® may be given as an injection in the muscle. The dose is based on the body weight.

Injection in the vein: Nozinan® may be given as an injection in the vein during surgery. The Nozinan® injection formulation is diluted with a glucose solution and injected slowly in a vein. The dose is based on the body weight.

Overdose:

If you have taken too much Nozinan®, immediately see your doctor or go to your nearest hospital emergency department. Show the doctor your bottle of tablets. 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.

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 call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	**Low blood pressure[a)]**		√	
Uncommon	**Allergic reactions[b)]**			√
See text below	**Blood disorders[c)]**		√	
	Cardiac disorders[d)]		√	
	Extrapyramidal reactions[e)]		√	
	Liver disorders[c)]		√	
	Lung disorders[c)]		√	
	Neuroleptic malignant syndrome[f)]		√	
	Tardive dyskinesia[g)]		√	

a) Low blood pressure. At the start of treatment with high oral doses or following an injection, some people may have low blood pressure and feel dizzy, especially when getting up from a lying or sitting position.

b) Allergic Reactions: You may also develop an allergy to Nozinan® for example skin rash, redness or itching. Consult your doctor immediately if you develop an allergy to Nozinan®.

c) Blood, liver and lung disorders have been associated with this class of drug. It is important that you tell your doctor at once about any unexplained symptom you might experience. Examples of this are soreness of the mouth, gums or throat or any symptoms of upper respiratory infection, unexplained fever, itching, flu-like symptoms, coughing, abdominal pain and jaundice.

d) Cardiac disorders: Uncommonly, Nozinan® may cause the heartbeat to become faster or irregular. Check with your doctor immediately if you experience any of these side effects.

e) Extrapyramidal reactions are rare and usually appear only after long-term therapy at high doses. The signs and symptoms of extrapyramidal reactions include tremor, muscle stiffness, body spasm, impairment of voluntary movement, upward eye rolling, exaggeration of reflexes or drooling. Tell your doctor immediately if you experience any of these side effects. Your medication might have to be reduced.

f) Neuroleptic malignant syndrome: Another possible serious unwanted effect is the neuroleptic malignant syndrome. Signs and symptoms of the neuroleptic malignant syndrome include severe muscle stiffness, increased sweating, fever, fast or irregular heartbeat, high or low blood pressure, difficult or fast breathing and confusion. If any of the above side effects occur, consult your doctor immediately.

g) Tardive dyskinesia may occur in some patients on long-term therapy or after they stop using Nozinan®. Signs of tardive dyskinesia include muscle twitching or uncontrolled movements of the mouth, tongue, face or jaw. In some patients, this side effect may not go away after they stop using Nozinan®. Tell your doctor immediately if you experience any muscle twitching or abnormal body movements.

Uncommon side effects include:

- Severe intestine problems
- Painful erection.

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˚ to 30˚C). Protect from exposure to light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:
Toll-free telephone: 1-866-234-2345
Toll-free fax: 1-866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9
NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

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.

This document plus the full product monograph is available upon request to the sponsor, sanofi-aventis Canada Inc., 2150 St Elzear Blvd. West, Laval, Quebec H7L 4A8, at:
1-800-265-7927

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