PRODUCT MONOGRAPH

Pr NITOMAN ®

(Tetrabenazine)

25mg Tablets

Monoamine Depleting Agent

Valeant Canada LP
2150 St-Elzear Blvd., West
Laval, Quebec H7L 4A8
Canada

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(tetrabenazine)

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PART I : ACTIONS AND CLINICAL PHARMACOLOGY

The central effects of NITOMAN (tetrabenazine) closely resemble those of reserpine, but it differs from the latter in having less peripheral activity and in being much shorter acting. In laboratory animals, tetrabenazine interferes with vesicular storage of biogenic amines, including dopamine as well as serotonin and noradrenaline; this effect is mainly limited to the brain. Dihydrotetrabenazine (HTBZ) is believed to be the principle active moiety, and it is thought that its clinical activity in movement disorders results from its action on monoamine storage in the brain. The duration of action of tetrabenazine ranges from 16 to 24 hours.

Tetrabenazine reversibly inhibits the human vesicular monoamine transporter type 2 (VMAT2) ($K_i \approx$ 100 nM), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. Human VMAT2 is also inhibited by dihydrotetrabenazine (HTBZ), a mixture of α -HTBZ and β -HTBZ. These major circulating tetrabenazine metabolites in humans, exhibit high *in-vitro* binding affinity to bovine VMAT2.

Tetrabenazine also has dopamine antagonistic effects, such as displacing ^{3}H-spiperone from striatal binding sites in vitro, and blocking dopaminergic inhibition of prolactin release in vitro and in vivo.

Pharmacokinetics:

Tetrabenazine has low and erratic bioavailability. It is extensively metabolised by first-pass metabolism. Little to no unchanged tetrabenazine can be detected in the urine. The major metabolite, dihydrotetrabenazine (HTBZ, a mixture of α -HTBZ and β -HTBZ), is formed by reduction of the C2 ketone group in tetrabenazine. α -HTBZ is O-dealkylated by CYP450 enzymes, principally CYP2D6, with some contribution of CYP1A2. β -HTBZ is O-dealkylated principally by CYP2D6. Following intravenous administration of radiolabelled tetrabenazine to humans, the radioactivity decreased to minimal levels within 10 hours and could not be detected three days later. Forty percent (40%) of total radioactivity was found in the urine within 24 hours and 2.5% in the feces. Fifty four percent (54%) of the total radioactivity was excreted after 48 hours.

INDICATIONS AND CLINICAL USE

NITOMAN (tetrabenazine) has been found useful in the treatment of hyperkinetic movement disorders such as Huntington's chorea, hemiballismus, senile chorea, tic and Gille's de la Tourette's syndrome and tardive dyskinesia.

Tetrabenazine is ***not*** indicated for the treatment of levodopa-induced dyskinetic/choreiform movements (See WARNINGS).

Tetrabenazine should only be used by (or in consultation with) physicians who are experienced in the treatment of hyperkinetic movement disorders.

CONTRAINDICATIONS

NITOMAN (tetrabenazine) is contraindicated:

- in patients with a known hypersensitivity to the drug or to any of the components of the formulation.
- in patients with currently untreated or inadequately treated episodes of clinical depression (See WARNINGS).
- In patients with a history of depression, including those with a current episode of depression being satisfactorily treated, Nitoman should not be used unless the patient is under the care of a supervising psychiatrist experienced with the patient's disorder and tetrabenazine's pharmacology
- if administered together with a monoamine oxidase inhibitor (MAOI). At least 14 days should elapse between the discontinuation of an MAOI and initiation of treatment with NITOMAN, as well as between the discontinuation of NITOMAN and the initiation of treatment with an MAOI (see PRECAUTIONS, *Drug Interactions*).
- in patients with impaired hepatic function.
- in patients taking reserpine.

WARNINGS

Depression:
NITOMAN may cause depression. Recognition of depression may be difficult because this condition may often be disguised by somatic complaints. The drug should be stopped immediately at the first signs or symptoms of depression. The depression can be profound, and the possibility of suicide should be kept in mind until the depression clears. Close observation of patients for the emergence of depression, suicidality or unusual changes in behaviour should accompany therapy. Patients, caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviours of concern promptly to the treating physician. There is no information on the safety or efficacy of antidepressant drug treatment in NITOMAN-induced depression.

- In patients with a history of depression, including those with a current episode of depression being satisfactorily treated, Nitoman should not be used unless the patient is under the care of a supervising psychiatrist experienced with the patient's disorder and tetrabenazine's pharmacology.

Parkinsonism:
NITOMAN can induce symptoms of parkinsonism, which are seen more frequently in the elderly and at relatively low doses. If a patient develops parkinsonism during treatment with NITOMAN, dose reduction should be considered; in some patients, discontinuation of therapy may be necessary.
Levodopa-induced dyskinetic/choreiform movements should be treated by reducing the dose of levodopa, and not by giving NITOMAN, since the latter exacerbates parkinsonian symptoms.

***Neuroleptic Malignant Syndrome (NMS*)**
Neuroleptic Malignant Syndrome (NMS) is a rare and potentially fatal symptom complex that has been reported in association with drugs that reduce dopaminergic transmission, including tetrabenazine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at the diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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

If the patient requires treatment with tetrabenazine after recovery from NMS, reintroduction of therapy should be carefully considered and slow titration initiated if required. The patient should be carefully monitored, since recurrences of NMS have been reported.

PRECAUTIONS

Psychomotor Impairment:
NITOMAN may cause drowsiness and orthostatic hypotension. Patients should be advised that until they learn how they respond to NITOMAN they should be careful doing activities that require them to be alert such as driving a car or operating machinery.

Use in Pregnancy and Lactation:
Tetrabenazine had no clear effects on embryo-fetal development when administered to pregnant rats throughout the period of organogenesis at oral doses up to 30 mg/kg/day (or 3 times the maximum recommended human dose [MRHD] of 100 mg/day on a mg/m^2 basis). Tetrabenazine had no effects on embryo-fetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day (or 12 times the MRHD on a mg/m^2 basis).
When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. The no-effect dose for stillbirths and postnatal mortality was 0.5 times the MRHD on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. NITOMAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Limited information indicates that NITOMAN is excreted in milk, therefore it should be avoided in breast-feeding mothers.

QT Interval

NITOMAN causes a slight prolongation of the QTc interval. Many drugs that cause QT/QTc prolongation are suspected to increase the risk of torsade de pointes. Generally, the risk of torsade de pointes increases with the magnitude of QT/QTc prolongation produced by the drug. In one randomized, placebo-controlled cross-over trial in healthy adult volunteers (n=51), the maximum time-matched, placebo-corrected increase in individually corrected QT (QTcI) following a single 50 mg oral tetrabenazine dose was 7.7 msec (90% CI 5.0-10.4), and 12.5 msec (90% CI 9.7-15.3) following a 400 mg moxifloxacin dose. The effect of tetrabenazine on the QTc interval under conditions of maximum exposure, e.g. in the presence of strong CYP2D6 inhibitors (see Drug Interactions), has not been evaluated in a thorough QT study.

NITOMAN should be avoided in patients at increased risk of experiencing arrhythmic events, such as patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, in patients with hypokalemia and hypomagnesemia and in concomitant use with drugs known to prolong the QT interval, including but not restricted to antipsychotic medications (e.g., chlorpromazine, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications.

Dysphagia

Dysphagia is a symptom of Huntington's Chorea. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. The latter symptom may be associated with aspiration pneumonia. In a 12-week, double-blind, placebo-controlled study and a 48-week follow-on open-label extension in patients with chorea associated with Huntington's disease, dysphagia was observed in ≤ 3% of NITOMAN treated patients. Some of the cases of dysphagia were associated with aspiration pneumonia. Whether these events were related to treatment is unknown. NITOMAN and other drugs that reduce dopaminergic transmission should be used with caution in patients at risk for aspiration pneumonia.

Hyperprolactinemia

Administration of a single 12.5 mg dose of NITOMAN in healthy volunteers resulted in a statistically significant increase of 4- to 5-fold in serum prolactin concentrations. Although amenorrhea, galactorrhea, gynecomastia and impotence can be caused by elevated serum prolactin concentrations, the clinical significance of elevated serum prolactin concentrations for most patients is unknown.

Since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependant *in-vitro*, tetrabenazine should be administered to patients with previously detected breast cancer only if the benefit outweighs the risk. Caution should be exercised when considering tetrabenazine treatment in patients with pituitary tumours.

Binding to Melanin-Containing Tissues

Since tetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that tetrabenazine may cause toxicity in these tissues after extended use.

Akathisia, Restlessness, and Agitation
In a 12-week, double blind, placebo-controlled study in patients with chorea associated with HD, akathisia was observed in 10 (19%) of NITOMAN-treated patients and 0% of placebo-treated patients. In an 80-week open label study, akathisia was observed in 20% of NITOMAN-treated patients. Akathisia was not observed in a 48-week open-label study. Patients receiving NITOMAN should be monitored for the presence of akathisia. Patients receiving NITOMAN should also be monitored for signs and symptoms of restlessness and agitation, as these may be indicators of developing akathisia. If a patient develops akathisia, the NITOMAN dose should be reduced; however, some patients may require discontinuation of therapy.

DRUG INTERACTIONS

CYP2D6 Inhibitors:
In vitro and *in vivo* studies indicate that the tetrabenazine metabolites α-DTBZ and β-DTBZ are substrates for CYP2D6. The effect of CYP2D6 inhibition on the pharmacokinetics of tetrabenazine and its metabolites was studied in 25 healthy subjects following a single 50 mg dose of tetrabenazine given the day prior to, and following, 8 days of administration of 20 mg daily of the strong CYP2D6 inhibitor paroxetine. There was an approximately 45% increase in C_{max} and an approximately 3.4-fold increase in $AUC_{0-\infty}$ for α-HTBZ in subjects given paroxetine and tetrabenazine, compared to tetrabenazine alone. For β-HTBZ, the C_{max} and $AUC_{0-\infty}$ were increased 2.7 and 9.6-fold respectively, in subjects given paroxetine and tetrabenazine, compared to tetrabenazine alone. The elimination half-life of α-HTBZ and β-HTBZ was approximately a mean of 14 hours when tetrabenazine was given with paroxetine, compared to means of 7 hours and 5 hours for α-HTBZ and β-HTBZ with tetrabenazine alone. Caution should be used when adding a CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine, duloxetine, terbinafine, amiodarone, or sertraline) to a patient already receiving a stable dose of tetrabenazine and a reduction in the dose of tetrabenazine should be considered. **(**see DOSAGE AND ADMINISTRATION**.**)
The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline on the pharmacokinetics of tetrabenazine has not been evaluated.

Levodopa:
Tetrabenazine exacerbates Parkinsonian symptoms, and thereby attenuates the effect of levodopa (See WARNINGS).

Antidepressants and Monoamine Oxidase Inhibitors (MAOIs):
Central excitation and possibly hypertension have occurred when tetrabenazine was added to existing therapy with desipramine or MAOIs.
There is no information on the safety and efficacy of antidepressant drugs, including MAOIs, in the treatment of tetrabenazine-induced depression. (see CONTRAINDICATIONS).

Neuroleptic Agents:
There is a potential for severe manifestations of dopamine deficiency, when administering NITOMAN concomitantly with neuroleptic agents (e.g. haloperidol, chlorpromazine, metoclopramide, olanzapine, risperidone, etc.). Neuroleptic malignant syndrome has been observed in isolated cases (see WARNINGS: Neuroleptic Malignant Syndrome).

Interaction with Alcohol
Patients should be advised that the concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence**.**

Reserpine
Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Caution should therefore be used when switching a patient from reserpine to NITOMAN. At least 20 days should elapse after stopping reserpine before starting NITOMAN. NITOMAN and reserpine should not be used concomitantly (see CONTRAINDICATIONS).

Drugs Known to Prolong the QT Interval
The use of NITOMAN with drugs known to prolong the QT interval should be avoided (see PRECAUTIONS, QT interval).

Special Populations:

Hepatic Impairment
In patients with mild to moderate hepatic impairment (Child-Pugh classes A and B), tetrabenazine plasma concentrations were similar to or higher than concentrations of α-HTBZ, reflecting the markedly decreased metabolism of tetrabenazine to α-HTBZ, and C_{max} for tetrabenazine increased 7- to 190-fold compared with detectable peak concentrations in subjects with normal liver function. An increase in t_{max} and elimination half-lives for α-HTBZ and β-HTBZ was observed in patients with hepatic impairment. The exposure to α -HTBZ and β -HTBZ was approximately 30-39% greater in patients with liver impairment than in age-matched controls. The effects of this increased exposure to tetrabenazine and its active metabolites on the safety and efficacy are unknown so that it is not possible to adjust the dosage of tetrabenazine in hepatic impairment to ensure safe use. Therefore, tetrabenazine is contraindicated in patients with hepatic impairment (see CONTRAINDICATIONS).

ADVERSE REACTIONS

The most commonly observed adverse reactions with NITOMAN (tetrabenazine) include, in decreasing order of frequency and observed during clinical use of the drug:

- Signs and symptoms of parkinsonism
- Drowsiness, fatigue, weakness
- Depression
- Anxiety, nervousness
- Insomnia
- Restlessness, akathisia
- Drooling
- Irritability, agitation
- Nausea, vomiting, epigastric pain
- Confusion, disorientation
- Hypotension
- Dizziness

Although NITOMAN has been in clinical use for a number of years, controlled clinical trials with the drug are limited.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms
For management of a suspected drug overdose, contact your regional Poison Control Centre.
Signs and symptoms of overdosage may include sweating and hypotension. Also reported were: acute dystonia, oculogyric crisis, nausea and vomiting, sedation, confusion, diarrhea, hallucinations, rubor and tremor. Overdose of NITOMAN may cause an increase in incidence and/or severity of the adverse reactions reported at therapeutic doses.

Management and Treatment
Cardiac rhythm and vital signs should be monitored. Treatment is symptomatic.

DOSAGE AND ADMINISTRATION

General
The initial dose should be low, and dosage should be titrated slowly according to the tolerance and responsiveness of the individual patient.

Adults
For most patients, an initial starting dose of 12.5 mg (half a tablet) two to three times a day is recommended. This can be increased by 12.5 mg a day weekly until the maximal tolerated and effective dose is reached for the individual, and may have to be up/down titrated depending on individual tolerance. For some patients, a slower titration may be more appropriate (see Special Populations, *CYP2D6 Poor Metabolizers*, and *Elderly and Debilitated Patients* below). In most cases the maximal tolerated dose will be 25 mg t.i.d. In very rare cases, a 200 mg dose has been reached (the maximum recommended dose in some publications).

If there is no improvement at the maximal tolerated dose in seven days, it is unlikely that NITOMAN will be of benefit to the patient, either by increasing the dose or by extending the duration of treatment.

Special Populations:

Hepatically Impaired Patients

The use of NITOMAN in patients with liver disease is contraindicated. (see CONTRAINDICATIONS and PRECAUTIONS, Special Populations)

CYP2D6 Poor Metabolizers:Although the pharmacokinetics of tetrabenazine and its metabolites in subjects who do not express the drug metabolizing enzyme CYP2D6 (poor metabolizers) have not been systematically evaluated, it is likely that the exposure to α-HTBZ and β-HTBZ would be increased compared to subjects who express the enzyme (extensive metabolizers), with $AUC_{0-\infty}$ increases similar to those observed in patients taking strong CYP2D6 inhibitors (approximately 3.4- and 9.6-fold, respectively; see DRUG INTERACTIONS). Caution in dosing should be exercised.

Elderly and Debilitated Patients:
No adequately controlled clinical studies have been performed in the elderly and/or debilitated patients. Clinical experience suggests that a reduced initial and maintenance dose should be used. Parkinsonian-like adverse reactions are relatively common in these patients and may be dose-limiting.

Children:
No adequately controlled clinical studies have been performed in children. Limited clinical experience suggests that treatment should be started at approximately half the adult dose, and titrated slowly and carefully according to tolerance and individual response.

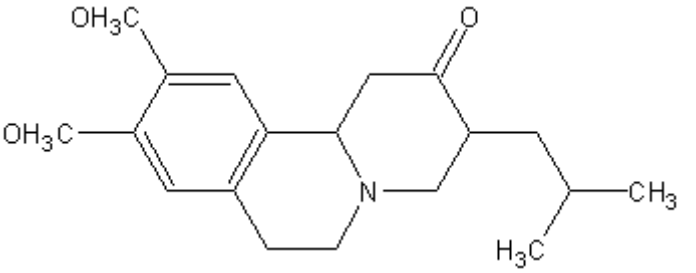
PART II: PHARMACEUTICAL INFORMATION

I. Drug Substance

Proper Name: tetrabenazine

Chemical Name: 2-oxo-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[a]-quinolizine

Structural Formula:



Molecular Formula: $C_{19}H_{27}NO_3$

Molecular Weight: 317.43

Description: White to slightly yellow crystalline powder

II. Composition: Each NITOMAN tablet contains 25 mg tetrabenazine, corn starch, lactose, talc, magnesium stearate, iron oxide.

III. Stability and Storage Recommendations: NITOMAN tablets should be stored in well-closed containers. Store at 15-30°C.

AVAILABILITY OF DOSAGE FORMS

Round, yellowish-buff tablets with CL 25 imprinted across one face and a single break bar on the other, containing 25 mg tetrabenazine. Bottles of 112 tablets.

Please Note: This product monograph does not contain toxicology information.

NITOMAN® is a registered trademark of Biovail Laboratories International (Barbados) S.R.L.

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PART III: CONSUMER INFORMATION
NITOMAN® 25 mg

This leaflet is Part III of a three-part Product Monograph and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NITOMAN®. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information before you start to take your medication, even if you have taken this drug before. Keep this information with your medicine in case you need to read it again.

ABOUT THIS MEDICATION

What the medication is used for:
NITOMAN® has been prescribed to you by your doctor to treat your symptoms of a movement disorder which causes jerky, irregular, uncontrollable movements, such as those seen in Huntington's chorea, hemiballismus, senile chorea, tic and Gille de la Tourette's syndrome, and tardive dyskinesia.

What it does:
NITOMAN® is one of a group of drugs called monoamine depleting agents. NITOMAN® is thought to interfere with storage of some chemicals in the brain such as dopamine which is associated with movement disorders.

When it should not be used?
Do not take NITOMAN® if you:
- are allergic to tetrabenazine
- are allergic to any of the non-medicinal ingredients listed below
- have symptoms of depression (eg.feeling sad, crying spells, worthless etc. – see Side Effects table on page 15)
- have had depression, in the past or are currently being treated for depression, unless you are under the care of a supervising psychiatrist experienced with your disorder and Nitoman.
- are taking or have recently taken Monoamine oxidase (MAO) inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide).
- are taking or have recently taken a medication used to treat high blood pressure called reserpine
- have liver problems

What the medicinal ingredient is:

Tetrabenazine

What the non-medicinal ingredients are:

Corn starch, lactose, talc, magnesium stearate, iron oxide.

What dosage forms it comes in:

25mg tablets

WARNINGS AND PRECAUTIONS

BEFORE you use NITOMAN® tell your doctor or pharmacist if you:
- have a current episode of depression or suicidal thoughts
- are taking any prescription or over-the-counter medications, or are planning on taking any prescription or over-the-counter medications during your therapy
- have liver problems.
- have heart disease including irregular heart beat
- have or have had breast cancer
- have or have had pituitary tumours
- have Parkinson's disease
- drink alcohol. It is best not to drink alcohol while taking NITOMAN®
- are pregnant, or thinking about becoming pregnant, or are breastfeeding

Depression:
NITOMAN® may cause depression in some patients. You and people close to you should watch for symptoms of depression (see table of Serious Side Effects below) and report to your doctor immediately should they occur.

Driving vehicles or using machinery:
NITOMAN® may cause drowsiness and low blood pressure. Driving, operating machinery, or performing other hazardous tasks should be avoided until the effect of NITOMAN® is known.

Trouble swallowing:
NITOMAN may increase the chance that you will have trouble swallowing. Contact your doctor if this happens.

Irregular heartbeat:
NITOMAN may cause changes in the electrical currents in your heart. Although these changes may be small, it may increase the risk of arrhythmias (irregular heart beats), especially if used in combination with other drugs that have the same effect, or if you already have certain heart conditions. If you feel a change in your heart beat, if you feel dizzy or faint, you should seek immediate

medical attention.

INTERACTIONS WITH THIS MEDICATION

You should tell your doctor if you are taking or have recently taken any medications (prescription, non-prescription or natural herbal) especially**:**

- monoamine oxidase (MAO) inhibitor antidepressants (e.g. phenelzine sulphate, moclobemide).
- antidepressants such as fluoxetine, paroxetine, quinidine, duloxetine, sertraline,
- antipsychotics such as thioridazine, chlorpromazine
- medicines for Parkinson's Disease such as levodopa, amantadine or orphenadrine.
- neuroleptic drugs such as haloperidol, chlorpromazine, metoclopramide.
- reserpine

You should consult your doctor before you start any new medicines or before you stop or change doses of any other medicine you are taking while taking NITOMAN.

PROPER USE OF THIS MEDICATION

Usual dose:

How to take NITOMAN®:

Adults
Take NITOMAN exactly as prescribed by your doctor.

- An initial starting dose of 12.5 mg two to three times a day is recommended. To obtain a 12.5 mg dose, the scored 25 mg tablet must be split with a pill cutter.
- This can be increased by 12.5 mg a day weekly until the maximal tolerated and effective dose is reached.
- In most cases the maximal tolerated dose will be 25 mg three times a day. In some cases higher doses may be prescribed.
- You should talk to your doctor before you stop taking your medication on your own. If you miss a dose and it is time or almost time for your next dose, take only the next scheduled dose and *do not* take 2 doses at once. If you miss several days contact your doctor as you may have to start with lower doses.

Elderly and Debilitated Patients
- Reduced initial and maintenance doses should be used. Your doctor will choose the appropriate dose

Chlidren
- Your doctor will decide the best dose.

Remember: This medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.

Overdose
The signs and symptoms of overdose may include drowsiness, sweating, low blood pressure, and feeling cold.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, NITOMAN® may cause some side effects. You may not experience any of them. However, some may be serious. Some of these side effects may be dose related. Consult your doctor if you experience these or other side effects, as the dose of NITOMAN® may have to be adjusted.

The most common side effects of NITOMAN®are:
- Signs and symptoms of Parkinsonism, such as tremors, difficulty starting or controlling movement, body stiffness, decrease in facial expressions, difficulty keeping your balance, speech problems, etc.
- Drowsiness, fatigue, weakness
- Depression
- Anxiety, nervousness
- Insomnia
- Restlessness, unable to sit or stand still
- Drooling
- Irritability, agitation
- Nausea, vomiting, stomach pain
- Confusion, disorientation
- Low blood pressure
- Dizziness

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist right away**		**Stop taking drug and seek immediate emergency medical assistance**
		Only if severe	**In all cases**	
Common	Depression (Symptoms may include: feeling sad, crying spells, sleeping a lot more or a lot less than usual, changes in weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family gatherings and activities with friends, reduced sex drive, and thoughts of death or suicide.		✓	
Common	Parkinsonism (Symptoms may include: tremors, difficulty starting or controlling movement, body stiffness, decrease in facial expressions, difficulty keeping your balance, speech problems.		✓	
Common	Akathisia (feeling restless and unable to sit or stand still	✓		
Common	Trouble swallowing (increased coughing may be the first sign that you are having trouble swallowing)		✓	
Frequency unknown	Allergic reactions [red and lumpy skin rash, hives, swelling, trouble breathing]			✓*
Frequency unknown	A state of confusion, reduced consciousness, high fever, rapid or irregular heartbeat, profuse sweating or pronounced muscle stiffness.			✓*
Frequency unknown	Symptoms of heart beat problems, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heat beat), fainting, or seizures.			✓*

* If you think you have these side effects, stop taking the drug.

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

HOW TO STORE IT

- Keep all medication out of the reach of children.
- Store NITOMAN® at room temperature (15-30°C).
- Keep container tightly closed.
- If your doctor tells you to stop taking NITOMAN® please return any left over medicine to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:** **Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.
This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor:
Valeant Canada LP
2150 St-Elzear Blvd., West
Laval, Quebec H7L 4A8

1-800-361-4261

This leaflet was prepared by Valeant Canada LP

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