PRODUCT MONOGRAPH

PrNITOMAN®
Tetrabenazine Tablets
25mg

Monoamine Depleting Agent

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West,
Laval, Quebec
H7L 4A8

Date of Revision:
October 1, 2020

Control #: 243154

PRODUCT MONOGRAPH

Pr NITOMAN®
Tetrabenazine Tablets
25mg

PART I: HEALTH PROFESSIONAL INFORMATION

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 metabolized 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 radiolabeled 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 (see PRECAUTIONS, General; PHARMACEUTICAL INFORMATION, Composition).
- in patients who are actively suicidal, or 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
- in patients taking 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 DRUG INTERACTIONS).
- in patients with impaired hepatic function.
- in patients taking reserpine (see DRUG INTERACTIONS). At least 20 days should elapse after stopping reserpine before starting NITOMAN.

WARNINGS

Depression and Suicidality
NITOMAN (tetrabenazine) can increase the risk of depression and suicidal thoughts and behavior (suicidality). When considering the use of NITOMAN the risks of depression and suicidality must be balanced with the clinical need for treatment. Close observation of patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior should accompany therapy. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviors of concern promptly to the treating physician.

Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation. NITOMAN is contraindicated in patients who are actively suicidal, in patients with currently untreated or inadequately treated depression. NITOMAN is also contraindicated in patients with a history of depression, including those with a current episode of depression being satisfactorily treated, unless the patient is under the care of a supervising psychiatrist experienced with the patient's disorder and tetrabenazine's pharmacology (see CONTRAINDICATIONS).

Depression, suicidal ideation and suicidal behaviors (suicidality) are known to occur in patients with Huntington's disease. In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with Huntington's disease, 10 of 54 patients (19%) treated with NITOMAN were reported to have an adverse event of depression or worsening depression compared to none of the 30 patients that received placebo. In two open-label studies patients were treated with NITOMAN for up to 48 weeks or up to 80 weeks (n=45 treated up to 80 weeks), the rate of depression/worsening depression was 35%. In all of the patients with chorea associated with Huntington's disease (n=187), one patient died by suicide, one patient attempted suicide, and six patients had suicidal ideation.

When considering the use of NITOMAN, the potential for an increase in risk of depression, worsening depression and suicidality should be balanced against the need for treatment. All patients treated with NITOMAN for hyperkinetic movement disorders should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with NITOMAN. There is no information on the safety or efficacy of antidepressant drug treatment in NITOMAN-induced depression.

Patients, their caregivers, and families should be informed of the risks of depression, worsening depression, and suicidality associated with NITOMAN, and should be instructed to report behaviors of concern promptly to the treating physician. Patients who express suicidal ideation should be evaluated immediately.

CYP2D6 Metabolizer Status
In vitro and in vivo studies indicate that the major active metabolites of tetrabenazine, α-HTBZ and β-HTBZ, are substrates for CYP2D6. 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, but exposure to α-HTBZ and β-HTBZ is expected to be increased compared to subjects who express the enzyme (extensive metabolizers). Exposure (AUC) in CYP2D6 poor metabolizers is expected to be similar to exposure in patients taking strong CYP2D6 inhibitors, with increases of approximately 3.4-fold for α-HTBZ and 9.6-fold for β-HTBZ, respectively (see DRUG INTERACTIONS). Therefore, dosing requirements may be influenced by a patient's CYP2D6 metabolizer status and use of concomitant medications which are strong CYP2D6 inhibitors.

For all patients the initial dose should be low, and dosage should be titrated slowly according to the tolerance and responsiveness of the individual patient. Treatment should be reassessed periodically in the context of the patient's underlying condition and their concomitant medications. (see DOSAGE AND ADMINISTRATION).

Clinical Worsening and Adverse Effects
Huntington's disease is a progressive disorder characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time. In a 12-week controlled trial, NITOMAN was also shown to cause slight worsening in mood, cognition, rigidity, and functional capacity. Whether these effects persist, resolve, or worsen with continued treatment is not known.

Prescribers should periodically re-evaluate the need for NITOMAN by assessing the effect on chorea and possible adverse effects, including depression and suicidality, cognitive decline, parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and disability.

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 with reintroduction of treatment.

Akathisia, Restlessness, and Agitation
NITOMAN may increase the risk of akathisia, restlessness an 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.

Sedation and Somnolence
Sedation is the most common dose-limiting adverse event of NITOMAN. Patients should not perform activities that require them to be alert such as driving a car or operating hazardous

machinery, until they are on a maintenance dose of NITOMAN and know how the drug affects them.

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 Cmax for tetrabenazine increased 7- to 190-fold compared with detectable peak concentrations in subjects with normal liver function. An increase in Tmax 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. Because the safety and efficacy of the increased exposure to tetrabenazine and other circulating metabolites are unknown, it is not possible to adjust the dosage of NITOMAN in hepatic impairment to ensure safe use. Therefore, tetrabenazine is contraindicated in patients with hepatic impairment (see CONTRAINDICATIONS).

CYP2D6 Poor Metabolizers

See WARNINGS, CYP2D6 Metabolizer Status; DOSAGE AND ADMINISTRATION, Special Populations.

Pregnant Women

There are no adequate and well-controlled studies of the use of NITOMAN in pregnant women to inform the drug-associated risk of adverse developmental outcomes. Studies in animals have shown reproductive toxicity of tetrabenazine and a major human metabolite of tetrabenazine at clinically relevant doses. The potential risk for humans is unknown. Therefore, NITOMAN is not recommended during pregnancy and in women of childbearing potential not using contraception.

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/m2 basis). Oral administration of a major human metabolite of tetrabenazine, 9-desmethyl-β-DHTBZ (8, 15, and 40 mg/kg/day), to pregnant rats throughout the period of organogenesis produced increases in embryofetal mortality at 15 and 40 mg/kg/day and reductions in fetal body weights at 40 mg/kg/day, which was also maternally toxic. 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. With oral administration of 9-desmethyl-β-DHTBZ (8, 15, and 40 mg/kg/day) to female rats from the beginning of organogenesis through the lactation period, increases in gestation duration, stillbirths, and offspring postnatal mortality (40 mg/kg/day); decreases in pup weights (40 mg/kg/day); and neurobehavioral (increased activity, learning and memory deficits) and reproductive (decreased litter size) impairment (15 and 40 mg/kg/day) were observed. Maternal

toxicity was seen at the highest dose. The no-effect dose for developmental toxicity in rats (8 mg/kg/day) was associated with plasma exposures (AUC) of 9-desmethyl-β-DHTBZ in pregnant rats lower than that in humans at the MRHD.

Breastfeeding
Limited information indicates that NITOMAN is excreted in milk. Therefore, the use of NITOMAN in breast-feeding mothers should be avoided.

Pediatrics (< 18 years of age)
See DOSAGE AND ADMINISTRATION.

Geriatrics (> 65 years of age)
The pharmacokinetics of tetrabenazine and its primary metabolites have not been systematically evaluated in geriatric subjects (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General
NITOMAN contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see CONTRAINDICATIONS; PHARMACEUTICAL INFORMATION, Composition).

QT Prolongation
In a 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.

Many drugs that cause QT/QTc prolongation have led to an increased risk of ventricular arrhythmias including torsade de pointes. Generally, the risk of torsade de pointes increases with the magnitude of QT/QTc prolongation produced by the drug.

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 electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders), and in patients with bradycardia. Concomitant use with drugs known to prolong the QT interval, including but not restricted to antipsychotic medications (e.g., chlorpromazine, thioridazine, haloperidol, ziprasidone), antibiotics (e.g., moxifloxacin), Class IA (e.g., quinidine, procainamide, disopyramide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications should be avoided (see DRUG INTERACTIONS).

Orthostatic Hypotension
Treatment emergent postural dizziness and syncope have been reported with NITOMAN at therapeutic doses and can be symptoms of orthostatic hypotension. In healthy subjects that received

single doses of 25 mg or 50 mg tetrabenazine, postural dizziness adverse events were very common and were reported within 1.5 to 4 hours after dosing. In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with Huntington's disease treatment emergent dizziness was reported in 4% of patients treated with NITOMAN compared to none on placebo, but blood pressure was not measured during these events. Monitoring of vital signs on standing should be considered for patients who may be at risk of hypotension.

Dysphagia
Dysphagia is a characteristic of Huntington's Chorea. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. Dysphagia 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. Chronic increase in serum prolactin levels (not evaluated in the tetrabenazine development program) has been associated with low levels of estrogen and increased risk of osteoporosis. If symptomatic hyperprolactinemia is suspected, appropriate laboratory testing should be done, and consideration should be given to discontinuation of tetrabenazine.

Since tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *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 tumors.

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. Chronic toxicity studies in a pigmented species, such as dogs, did not include ophthalmologic or microscopic examination of the eye. There are insufficient data from monitoring in humans to exclude ophthalmic toxicity during long-term exposure.

The clinical relevance of tetrabenazine's binding to melanin-containing tissues is unknown. Although there are no specific recommendations for periodic ophthalmic monitoring, prescribers should be aware of the possibility of ophthalmologic effects after long-term exposure.

DRUG INTERACTIONS

CYP2D6 Inhibitors

In vitro and *in vivo* studies indicate that the major active metabolites of tetrabenazine α-HTBZ and β-HTBZ 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 may be needed **(**see DOSAGE AND ADMINISTRATION, Special Populations)

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, Parkinsonism).

Monoamine Oxidase Inhibitors (MAOIs) and Antidepressants

NITOMAN is contraindicated in patients taking MAOIs. NITOMAN should not be used in combination with an MAOI due to the risk of hypertensive crisis. At least 14 days should elapse between discontinuing therapy with 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 CONTRAINDICATIONS).

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

The risk of neuroleptic malignant syndrome and extrapyramidal disorders (e.g., parkinsonism, akathisia) may be increased, when administering NITOMAN concomitantly with dopamine antagonists or antipsychotics (e.g. haloperidol, chlorpromazine, metoclopramide, olanzapine, risperidone, etc.). Neuroleptic malignant syndrome has been observed in isolated cases in patients treated with NITOMAN (see WARNINGS: *Parkinsonism; Neuroleptic Malignant Syndrome, Akathisia, Restless and Agitation*).

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

Reserpine
Concomitant use of tetrabenazine and reserpine is contraindicated. 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 (see CONTRAINDICATIONS).

Anti-arrhythmic Drugs and Other QTc-Prolonging Drugs
NITOMAN prolongs the QTc interval by approximately 8 msec (see PRECAUTIONS, QT interval). Because of the potential for additive effects on QTc interval prolongation, the concomitant use of NITOMAN with Class Ia (e.g., disopyramide, procainamide, quinidine) or Class III (e.g., amiodarone, sotalol) anti-arrhythmic drugs and other drugs that are associated with QTc interval prolongation should be avoided.

Chemical/pharmacological classes in which some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes include: Class 1c antiarrhythmics (e.g., flecainide, propafenone); antipsychotics (e.g., chlorpromazine, haloperidol); antidepressants (e.g., fluoxetine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, tacrolimus); quinolone antibiotics (e.g., moxifloxacin, ciprofloxacin); antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole); domperidone; 5-HT3 receptor antagonists (e.g., ondansetron); kinase inhibitors (e.g., sunitinib); histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol).

Antihypertensive Drugs and Beta-Blockers
The concomitant use of NITOMAN with antihypertensive drugs and beta-blockers may increase the risk of orthostatic hypotension (see PRECAUTIONS, Orthostatic Hypotension).

ADVERSE REACTIONS

Although NITOMAN has been in clinical use for a number of years, controlled clinical trials with the drug are limited. In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with Huntington's disease dose escalation was discontinued or dosage of study drug was reduced in 28 of 54 patients randomized to NITOMAN because of one or more of the following adverse events (listed in decreasing order of frequency): sedation, akathisia, parkinsonism, depression, anxiety, fatigue and diarrhea.

Clinical Trial Adverse Reactions

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

- Drowsiness, weakness (sedation /somnolence)

- Fatigue
- Insomnia
- Irritability
- Dizziness
- Depression
- Restlessness, akathisia
- Anxiety/anxiety aggravated
- Nausea, vomiting, epigastric pain
- Signs and symptoms of parkinsonism

Post-Market Adverse Reactions

- Tremor
- Worsening aggression
- Pneumonia
- Hyperhidrosis
- Skin rash
- Drooling
- Agitation
- Confusion, disorientation
- Hypotension
- Weight increased
- Increased appetite

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

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

Treatment should consist of general measures employed in the management of overdosage with any CNS-active drug. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital signs should be monitored.

In managing overdosage, the possibility of multiple drug involvement should always be considered.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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. Once a stable dose has been achieved, treatment should be reassessed periodically in the context of the patient's underlying condition and their concomitant medications.

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 slowly by 12.5 mg a day at weekly intervals, until the maximal tolerated and effective dose is reached for the individual and may have to be up/down titrated depending on individual tolerance (see ADVERSE REACTIONS). For some patients, a slower titration may be more appropriate (see Special Populations, *CYP2D6 Poor Metabolizers*, and *Geriatrics* 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.

Re-initiation of NITOMAN After Treatment Interruption
Following treatment interruption of greater than five days, NITOMAN should be re-titrated when resumed. For short-term treatment interruption of less than five days, NITOMAN can be resumed at the previous maintenance dose without titration.

Special Populations

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

CYP2D6 Poor Metabolizer
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 (see WARNINGS, CYP2D6 Metabolizer Status).

Geriatrics (> 65 years of age)
The pharmacokinetics of tetrabenazine and its primary metabolites have not been systematically evaluated in geriatric subjects. Clinical experience suggests that a reduced initial and maintenance dose should be used. Parkinsonian-like adverse reactions are relatively common in geriatric and debilitated patients and may be dose-limiting.

Pediatrics (< 18 years of age)
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.

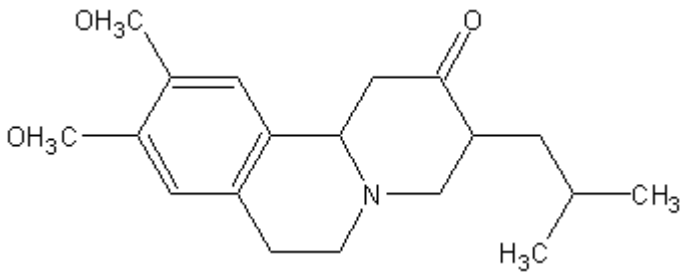
PART II: PHARMACEUTICAL INFORMATION

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 g/mol

Physicochemical Properties

Description: White to slightly yellow crystalline powder

Composition

Each NITOMAN tablet contains 25 mg Tetrabenazine, Corn Starch, Lactose, Talc, Magnesium Stearate and Iron Oxide.

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.

BIBLIOGRAPHY

1. Asher, SW, Aminoff, MJ. Tetrabenazine and movement disorders. Neurology 1981; 31:1051-4.

2. Jankovic, J. Treatment of hyperkinetic movement disorders with tetrabenazine: A double-blind crossover study. Ann Neurol 1982; 11(1):41-7.

3. Mikkelsen, BO. Tolerance of tetrabenazine during long-term treatment. Acta Neurol Scand 1983; 68:57-60.

4. Roberts, MS et al. The pharmacokinetics of tetrabenazine and its hydroxy metabolite in patients treated for involuntary movement disorders. Eur J Clin Pharmacol 1986; 29:703-8.

5. Mehvar, R et al. Pharmacokinetics of tetrabenazine and its major metabolite in man and rat. Bioavailability and dose dependency studies. Drug Metab Dispos 1987; 5(2):250-5.

6. Jankovic, J, Orman, J. Tetrabenazine therapy of dystonia, chorea, tics and other dyskinesias. Neurology 1988; 38(3):391-4.

7. Bressman SB, Greene PE. Treatment of hyperkinetic movement disorders. Clin Neuropharmacology 1990; 8(1):51-75.

8. Mateo D, Munoz-Blanco JL, Gimenez-Roldan S. Neuroleptic Malignant syndrome related to tetrabenazine introduction and haloperidol discontinuation in Huntington's disease. Clin Neuropharmacol 1992; 15(1):63-8.

PART III: CONSUMER INFORMATION

PrNITOMAN®
Tetrabenazine Tablets
25mg

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 (e.g. 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 and 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 history of or 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. You should not take NITOMAN if you are taking reserpine or if you are taking a monoamine oxidase (MAO) inhibitor.
- have liver problems.
- have heart disease including irregular heart beat
- have or have had breast cancer
- have or have had pituitary tumors
- 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
- if you have rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption because NITOMAN contains lactose.

Depression:
NITOMAN may cause depression, thoughts of suicide or death or suicidal behavior in some patients. You and people close to you should watch for changes in your mood, or if you start to have thoughts about hurting yourself (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 you know how NITOMAN affects you.

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. These changes may increase the risk of arrhythmias (irregular heartbeats), 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 (e.g. phenelzine sulphate, moclobemide)
- antidepressants such as fluoxetine, paroxetine, duloxetine, sertraline

- medicines that treat an irregular heartbeat such as quinidine, procainamide, amiodarone, sotalol
- antipsychotics or dopamine antagonists such as thioridazine, chlorpromazine haloperidol, metoclopramide, olanzapine, risperidone
- medicines for Parkinson's Disease such as levodopa, amantadine or orphenadrine.
- 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 each week 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.

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

Children
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, symptoms may include dizziness when standing up
- Dizziness
- Weight increased
- Increased appetite

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.		✓	
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]			✓*

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**	
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 heart beat), fainting, or seizures.			✓*
Frequency unknown	Thoughts of death or suicide		✓*	

* 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 leftover medicine to your pharmacist.

Reporting Side Effects

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

Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/news/media-room/advisories-warnings/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or

Calling toll-free at 1-866-234-2345.

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

MORE INFORMATION

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:

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West,
Laval, Quebec
H7L 4A8
1-800-361-4261

This leaflet was prepared by Bausch Health, Canada Inc.

Last Revised: October 1, 2020