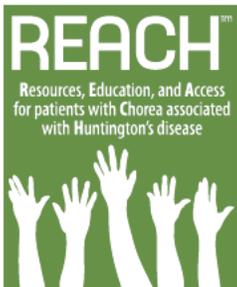


Prescribing Xenazine® (tetrabenazine) Tablets

A Healthcare Professional Guide



This booklet contains important safety information about the following serious risks of Xenazine:

- Drug-Associated Depression and Suicidality
- Need for Proper Titration and Dosing
- Drug–Drug Interactions With CYP2D6 Inhibitors

This booklet is required and approved by the FDA as part of the Xenazine Risk Evaluation and Mitigation Strategy (REMS). A REMS is a strategy to manage known or potential serious risks associated with a drug to ensure that the benefits of the drug outweigh its risks.

Please see Important Safety Information, including Boxed Warning about the increased risk of depression and suicidality, on page 2. Please see full Prescribing Information beginning on page 11.

Xenazine®
(tetrabenazine)
12.5 and 25 mg Tablets

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Please see full Prescribing Information beginning on page 11.

Important Safety Information About Xenazine

XENAZINE® (tetrabenazine) Tablets

Indications and Usage:

XENAZINE is indicated for the treatment of chorea associated with Huntington's disease.

Important Safety Information:

WARNING: DEPRESSION AND SUICIDALITY

See full prescribing information for complete boxed warning.

- **Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease.**
- **Balance risks of depression and suicidality with the clinical need for control of choreiform movements when considering the use of XENAZINE.**
- **Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior.**
- **Inform patients, caregivers, and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician.**
- **Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation.**
- **XENAZINE is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.**

- XENAZINE is also contraindicated in patients who have impaired hepatic function or are taking monoamine oxidase inhibitors (MAOIs) or reserpine. XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. At least 20 days should elapse after stopping reserpine before starting XENAZINE.
- Prescribers should periodically re-evaluate the need for XENAZINE in their patients by assessing the beneficial effect on chorea and possible adverse effects including worsening mood, cognition, rigidity, and functional capacity. XENAZINE should be titrated slowly over several weeks for a dose that is appropriate for each patient.
- Before a dose greater than 50 mg is administered, the patient's CYP2D6 metabolizer status should be determined. Do not exceed 50 mg/day or 25 mg/dose if XENAZINE is administered with a strong CYP2D6 inhibitor.
- XENAZINE therapy should be retitrated if there is a treatment interruption of greater than 5 days, or a treatment interruption occurring due to a change in the patient's medical condition or concomitant medications.

- A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with XENAZINE. 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 management of NMS should include immediate discontinuation of XENAZINE and other drugs not essential to concurrent therapy.
- XENAZINE can also cause other serious side effects including: akathisia, restlessness, agitation, parkinsonism, and sedation/somnolence. These side effects may require a dose reduction or discontinuation of XENAZINE. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension. Dysphagia has also been reported with use of XENAZINE; some cases of dysphagia were associated with aspiration pneumonia.
- QT prolongation—related arrhythmias have been reported with use of XENAZINE. XENAZINE should not be used in combination with drugs known to prolong QTc (which in certain circumstances can lead to torsades de pointes and/or sudden death), in patients with congenital long QT syndrome, or in patients with a history of cardiac arrhythmias. A potentially irreversible syndrome of involuntary, dyskinetic movements called tardive dyskinesia (TD) may develop in patients treated with neuroleptic drugs. If signs and symptoms of TD appear in a patient treated with XENAZINE, drug discontinuation should be considered. Adverse reactions associated with XENAZINE, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists.
- XENAZINE elevates serum prolactin concentrations. XENAZINE may induce sedation/somnolence which may impair the ability to drive or operate dangerous machinery. Alcohol or other sedating drugs can worsen sedation/somnolence.
- Some adverse events such as depression, fatigue, insomnia, sedation/somnolence, parkinsonism, and akathisia may be dose-dependent. If the adverse effect does not resolve or decrease, consideration should be given to lowering or discontinuing XENAZINE. The most commonly reported adverse events with XENAZINE compared to placebo were sedation/somnolence (31% vs 3%), fatigue (22% vs 13%), insomnia (22% vs 0%), depression (19% vs 0%), akathisia (19% vs 0%), anxiety (15% vs 3%), and nausea (13% vs 7%).

For more information, please see the full Prescribing Information, including Boxed Warning, the Medication Guide, or go to www.XenazineUSA.com.

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Considerations When Treating HD Chorea With Xenazine

The efficacy of Xenazine as a treatment for chorea associated with HD was established primarily in a 12-week, multicenter, randomized, double-blind, placebo-controlled clinical trial.

The most common adverse events associated with Xenazine use include sedation/somnolence, fatigue, insomnia, depression, anxiety, akathisia or restlessness, and nausea (see ADVERSE REACTIONS in Xenazine Prescribing Information).

Xenazine 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 unknown. Proper use of Xenazine requires attention to all facets of the underlying disease process over time (see CLINICAL STUDIES in Xenazine Prescribing Information).

It may be difficult to distinguish between drug-induced adverse events and progression of the underlying disease process. For this reason, dose reductions or periodic treatment interruptions may help distinguish between the 2 possibilities. In some patients, underlying chorea itself may improve over time, decreasing the need for Xenazine (see WARNINGS in Xenazine Prescribing Information).

Periodic reevaluations should include special attention to developing depression, cognitive decline, parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and functional disability (see WARNINGS in Xenazine Prescribing Information).

The Risk for Suicidality and/or New or Worsening Depression

Patients with HD are at increased risk for depression and suicidal ideation and behavior (suicidality). Xenazine can increase these risks. All patients treated with Xenazine should be observed closely for new or worsening depression or suicidality.

Suicide rates for symptomatic HD patients were reported in one study to be 4 to 5 times higher than in the general US population¹; they were found to be 7 to 12 times higher in a more recent study.² Over 25% of patients attempt suicide at some point during the course of the illness.

Suicide risk is especially high among HD patients at the following times²:

- At the onset of signs or symptoms of disease
- When activities become restricted or patients lose the ability to independently perform activities of daily living

Depression or worsening of depressive symptoms occurs with increased frequency in patients receiving Xenazine. In a 12-week, double-blind study in patients with chorea of HD, 10 of 54 patients (19%) treated with Xenazine were reported to have an adverse event of depression compared with none of the 30 placebo-treated patients. Patients at risk for or with a history of depression should be monitored carefully, as they may be at increased risk for suicidal behavior.

Patients and their families and caregivers should be alerted to the risks of depression, worsening depression, and suicidality associated with Xenazine and should be instructed to report the emergence of signs and symptoms promptly to their physician.

Recognizing Symptoms of Depression or Suicidality³

Before patients can be prescribed Xenazine, it is important for the prescriber to recognize whether or not the patient suffers from depression or suicidality. Prescribers who are alert to the warning signs of psychiatric disorders can guide patients to receive the help they need.

The following is an overview of the signs and symptoms of depression or suicidality:

- Persistent sadness, anxiety, or feeling of emptiness
- Feelings of guilt, hopelessness, worthlessness, helplessness, or pessimism
- Loss of pleasure from activities that were once enjoyed
- Social withdrawal
- Fatigue or loss of energy
- Difficulty concentrating, remembering details, or making decisions
- Change in sleep pattern
- Change in appetite
- Physical problems that do not respond to treatment
- Restlessness
- Irritability
- Suicidal ideation
- Suicidal intent or plan

Talk with your patients about the specific signs and symptoms of depression at every visit.

Initiating Treatment With Xenazine

Individualized Dosing

Xenazine is supplied in 2 dosage strengths: 12.5-mg white tablet and 25-mg yellowish-buff (scored) tablet.

- The dose of Xenazine should be individualized.
- The starting dose should be 12.5 mg once daily in the morning.
- One week later, the dose should be increased to 25 mg per day (12.5 mg in the morning and 12.5 mg in the evening 12 hours later).
- The daily dose should then continue to be increased at weekly intervals by 12.5-mg increments until satisfactory control of chorea is achieved or adverse events occur.
- If a dose of 37.5 mg per day or greater is needed, it should be given in a 3-times-daily regimen. The Initial Dosing Plan below describes the recommended titration schedule.

	Week 1	Week 2	Week 3
Morning	12.5 mg	12.5 mg	12.5 mg
Afternoon	–	–	12.5 mg
Evening	–	12.5 mg	12.5 mg
Total Daily Dose	12.5 mg	25 mg	37.5 mg

Before prescribing Xenazine, healthcare professionals should talk to the patient and caregiver about what they should do if the patient misses a dose. Reemergence of chorea may occur within 12 to 18 hours after the last dose of Xenazine.

Retitration of Xenazine should occur following any treatment interruption lasting longer than 5 days. If treatment with Xenazine is resumed, it should be retitrated according to the Initial Dosing Plan described above (see DOSAGE AND ADMINISTRATION in Xenazine Prescribing Information).

Testing for CYP2D6 and Recommendations for Dosing Above 50 mg per Day

Before patients are given a daily dose greater than 50 mg, they should be tested for the CYP2D6 drug-metabolizing enzyme to determine whether they are poor, extensive, or intermediate metabolizers. When a dose of tetrabenazine is given to poor metabolizers, exposure will be substantially higher than it would be in extensive metabolizers. The dosage should therefore be adjusted according to the patient's CYP2D6 metabolizer status by limiting the dose to 50 mg in patients who are CYP2D6 poor metabolizers (see CLINICAL PHARMACOLOGY; WARNINGS - Laboratory Tests; and DOSAGE AND ADMINISTRATION in Xenazine Prescribing Information).

- For poor metabolizers, the maximum recommended single dose is 25 mg, and the maximum recommended daily dose is 50 mg.
- For extensive or intermediate metabolizers, the maximum recommended single dose is 37.5 mg, and the maximum recommended daily dose is 100 mg.

Potential Drug Interactions With CYP2D6 Inhibitors

- Caution should be used when adding therapy with a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, or quinidine) to patients already receiving a stable dose of Xenazine; a reduction in Xenazine dose may be necessary. The daily dose of Xenazine should not exceed 50 mg per day and the maximum single dose should not exceed 25 mg in patients taking strong CYP2D6 inhibitors (see PRECAUTIONS - Drug Interactions; DOSAGE AND ADMINISTRATION; and SPECIAL POPULATIONS in Xenazine Prescribing Information).
- To initiate treatment with Xenazine in patients on a stable dose of a strong CYP2D6 inhibitor, the dosing recommendations for poor metabolizers of CYP2D6 should be followed. The effect of moderate or weak CYP2D6 inhibitors, such as duloxetine, terbinafine, amiodarone, or sertraline, has not been evaluated (see CLINICAL PHARMACOLOGY and PRECAUTIONS in Xenazine Prescribing Information).

Monitoring Therapy With Xenazine

As described in Section II – Considerations When Treating HD Chorea With Xenazine, healthcare professionals should periodically reevaluate the need for Xenazine in their patients by assessing the beneficial effect on choreiform movements and possible adverse events, including depression, cognitive decline, parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and disability.

It may be difficult to distinguish between drug-induced adverse events and the progression of the underlying disease; in such a case, decreasing the dose or stopping the drug may help the clinician distinguish between the 2 possibilities. In some patients, underlying chorea itself may improve over time, decreasing the need for Xenazine (see WARNINGS in Xenazine Prescribing Information).

Treatment with Xenazine can be discontinued without tapering. Reemergence of chorea may occur within 12 to 18 hours after the last dose of Xenazine (see DOSAGE AND ADMINISTRATION - Discontinuation of Treatment With Xenazine in Xenazine Prescribing Information).

Patients should be closely monitored, especially during titration to a maintenance dose. In addition to depression, suicidality, individualized dosing, and potential CYP2D6 inhibitors, the following are important adverse events that may occur with Xenazine (see Section I – Important Safety Information About Xenazine and Section VII – Xenazine Prescribing Information).

If adverse events such as akathisia, restlessness, parkinsonism, depression, insomnia, anxiety, or sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing Xenazine treatment or initiating other specific treatment (eg, antidepressants)(see DOSAGE AND ADMINISTRATION - Dosing Recommendations up to 50 mg per Day in Xenazine Prescribing Information).

If depression or suicidality occurs, the dose of Xenazine should be reduced. Initiating treatment with or increasing the dose of a concomitant antidepressant may also be useful. In patients with new-onset depression who require antidepressants that are strong CYP2D6 inhibitors (such as paroxetine and fluoxetine), the total dose of Xenazine may need to be reduced in patients who are maintained on a stable dose of Xenazine. If depression or suicidality does not resolve, consideration should be given to discontinuing treatment with Xenazine (see PRECAUTIONS and DOSAGE AND ADMINISTRATION in Xenazine Prescribing Information).

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially fatal symptom complex that has been reported in association with Xenazine and other drugs that reduce dopaminergic transmission. 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 management of NMS should include:

- Immediate discontinuation of Xenazine and other nonessential drugs
- Intensive symptomatic treatment and medical monitoring
- 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 Xenazine after recovery from NMS, the potential reintroduction of treatment should be carefully considered. The patient should be carefully monitored because recurrences of NMS have been reported.

Although no cases of NMS occurred in controlled clinical trials with Xenazine, cases of NMS have been reported in the foreign postmarketing setting prior to US approval (see PRECAUTIONS in Xenazine Prescribing Information).

Please see Important Safety Information, including Boxed Warning about the increased risk of depression and suicidality, on page 2. Please see full Prescribing Information beginning on page 11.

Other Precautions

- **Akathisia, restlessness, and agitation.** Patients receiving Xenazine should be monitored for the presence of akathisia or signs and symptoms of restlessness and agitation. If a patient develops akathisia, the Xenazine dose should be reduced; however, some patients may require discontinuation of therapy.
- **Parkinsonism.** As with other dopamine-depleting drugs, Xenazine can cause parkinsonism. Because rigidity can develop as part of the underlying disease process in HD, it may be difficult to distinguish between this drug-induced adverse event and progression of the underlying disease process. Drug-induced parkinsonism has the potential to cause more functional disability than untreated chorea for some patients with HD. If a patient develops parkinsonism during treatment with Xenazine, dose reduction should be considered; in some patients, discontinuation of therapy may be necessary.
- **Dysphagia.** Dysphagia is a component of HD. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. Dysphagia may be associated with aspiration pneumonia.
- **Sedation and somnolence.** Sedation is the most common dose-limiting adverse event with Xenazine. Patients should be advised that the concomitant use of alcohol or other sedating drugs may have an additive effect and worsen sedation and somnolence.
- **QTc prolongation.** Xenazine causes a small increase (about 8 msec) in the corrected QT (QTc) interval. QTc prolongation can lead to development of torsades de pointes–type ventricular tachycardia with the risk increasing as the degree of prolongation increases (see CLINICAL PHARMACOLOGY - Pharmacodynamics in Xenazine Prescribing Information). The use of Xenazine should be avoided in combination with other drugs that are known to prolong QTc, including antipsychotic medications (eg, chlorpromazine, thioridazine, ziprasidone), antibiotics (eg, moxifloxacin), Class 1A (eg, quinidine, procainamide) and Class III (eg, amiodarone, sotalol) antiarrhythmic medications, or any other class of medications known to prolong the QTc interval.
- **Concomitant use of neuroleptic drugs.** Patients taking neuroleptic (antipsychotic) drugs (eg, haloperidol, chlorpromazine, risperidone, olanzapine, thioridazine, ziprasidone) were excluded from clinical studies during the Xenazine development program. Adverse reactions associated with Xenazine, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists.
- **Interaction with alcohol and sedating drugs.** Patients should be advised that the concomitant use of alcohol or other sedating drugs might have additive effects and worsen sedation and somnolence (see INFORMATION FOR PATIENTS in Xenazine Prescribing Information).
- **Hypotension and orthostatic hypotension.** Xenazine should be used with caution in patients with known cardiovascular disease (eg, heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).
- **Hyperprolactinemia.** Xenazine elevates serum prolactin concentrations in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance when prescribing Xenazine for patients with previously detected breast cancer.
- **Tardive dyskinesia.** Tardive dyskinesia (TD) is a potentially irreversible syndrome of involuntary, dyskinetic movements that may develop in patients treated with neuroleptic drugs. Xenazine has a mechanism similar to that of neuroleptic drugs known to cause TD. Xenazine also causes extrapyramidal symptoms (eg, parkinsonism, akathisia) known to be caused by neuroleptic drugs. Therefore, physicians should be aware of the possible risk of this clinical syndrome.

Although the prevalence of TD in patients treated with neuroleptics appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. The risk of developing TD and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of the neuroleptic administered to the patient increase. There is no known treatment for established TD, although the syndrome may remit partially or completely if the drug is withdrawn.

See PRECAUTIONS in Xenazine Prescribing Information for additional information.

Xenazine Educational Materials

In addition to the Xenazine Prescribing Information, specialized educational materials are available to prescribing healthcare professionals, patients, and caregivers to help educate about the benefits and risks of Xenazine therapy.

Information for Healthcare Professionals

1. Prescribing Xenazine: A Healthcare Professional Guide

Describes the key benefits and risks of Xenazine therapy.

2. Initial Dosing Plan

Highlights Xenazine titration through Week 3. After Week 3, the healthcare professional should provide an individualized dosing plan for each patient; the healthcare professional should complete the card accordingly.

3. Toll-Free Xenazine Information Center

A toll-free Xenazine information line is available to provide healthcare professionals and patients with information about Xenazine (1-888-882-6013).

Information for Patients and Caregivers

The following materials should be provided by prescribing healthcare professionals to educate patients, family members, and/or caregivers about Xenazine:

1. What You Need to Know About Xenazine: Patient/Caregiver Counseling Guide

This guide explains Xenazine therapy, dosing, and potential adverse events at a level that can be easily understood by the majority of Xenazine patients and/or caregivers.

2. Medication Guide

Provided to patients with every new and refilled prescription of Xenazine.

3. Initial Dosing Plan

Provided by the prescribing healthcare professional to instruct patients on their dosing.

What to Discuss With Your Patients

Xenazine treatment should not be started before the patient has been counseled on the Important Safety Information about Xenazine. A Medication Guide will be dispensed by the Specialty Pharmacy to every patient with each new and refilled prescription. A copy of the Medication Guide should be provided to the patient prior to initiation of treatment. The healthcare professional should also distribute *What You Need to Know About Xenazine: Patient/Caregiver Counseling Guide*. The Initial Dosing Plan should be filled in by the healthcare professional for each patient, as appropriate.

The following information should be discussed with patients and caregivers before initiating treatment with Xenazine:

- Patients and their families should be informed that Xenazine may increase the risk of suicide in some people. Patients and their families should be encouraged to be alert to the emergence of suicidal ideation. These symptoms should be reported immediately to the patient's healthcare professional.
- Patients and their families should be informed that Xenazine may cause depression or may worsen preexisting depression. Patients and their families should be encouraged to be alert to the emergence of sadness, worsening of depression, withdrawal, insomnia or hypersomnia, irritability, hostility (aggressiveness), akathisia (psychomotor restlessness), anxiety, agitation, fatigue, feelings of worthlessness or excessive guilt, or diminished ability to think or concentrate. These symptoms should be reported immediately to the patient's healthcare professional.
- Patients and their families should be told that the dose of Xenazine will be titrated up slowly to the dose that reduces chorea and is tolerated. Sedation, akathisia, parkinsonism, depression, and difficulty swallowing may occur. These symptoms should be reported immediately to the patient's healthcare professional.
- Patients and their families should be told that Xenazine may induce sedation and somnolence and may therefore impair the ability to perform tasks that require complex motor and mental skills. Patients should be advised that until they learn how they respond to Xenazine, they should be careful doing activities that require that they be alert, such as driving a car or operating machinery.
- Patients and their families should be advised that alcohol and sedating drugs may exacerbate the sedation induced by Xenazine.
- Patients and their families should be advised to notify their healthcare professionals if the patient becomes pregnant or intends to become pregnant during treatment.
- Patients and their families should be advised to notify their healthcare professionals if the patient is breast-feeding an infant during treatment.
- Patients and their families should be advised to notify their healthcare professionals of all medications they are taking and to consult their healthcare professionals before they start, stop, or change the dose of any medications.

References:

1. Bird TD. Outrageous fortune: the risk of suicide in genetic testing for Huntington disease. *Am J Hum Genet.* 1999;64:1289-1292.
2. Paulsen JS, Hoth KF, Nehl C, Stierman L, with the Huntington Study Group. Critical periods of suicide risk in Huntington's disease. *Am J Psychiatry.* 2005;162:725-731.
3. National Institute of Mental Health, National Institutes of Health, US Department of Health and Human Services. *Depression.* Bethesda, MD: National Institute of Mental Health; 2007. NIH publication 07-3561.