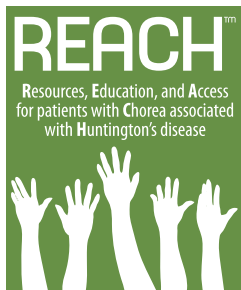


Prescribing Xenazine® (tetrabenazine) Tablets

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 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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Section I:

Important Safety Information About Xenazine

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.

• Neuroleptic malignant syndrome (NMS), akathisia, agitation, parkinsonism, dysphagia and aspiration pneumonia, and 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 and somnolence (sleepiness or drowsiness) and may impair the ability to drive or operate dangerous machinery. Alcohol or other sedating drugs can worsen sedation and 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 full prescribing information, including Boxed Warning, 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).

Although Xenazine was shown to decrease the HD chorea, it 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 or a treatment interruption due to a change in the patient's medical condition or concomitant medications. 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 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; the daily dose of Xenazine should be halved (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 intolerable 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 should be halved. 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).

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. Because dysphagia may be associated with aspiration pneumonia, Xenazine and other drugs that reduce dopaminergic transmission should be used with caution in patients with HD at risk for 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 drugs (eg, haloperidol, chlorpromazine, risperidone, olanzapine) 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.

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

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 well 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.

Xenazine Full Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XENAZINE safely and effectively. See full prescribing information for XENAZINE.

Xenazine® (tetrabenazine) Tablet, for Oral Use

Initial U.S. Approval: 2008

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. (5.3)
- Balance risks of depression and suicidality with the clinical need for control of choreiform movements when considering the use of XENAZINE. (5.1)
- Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior. (5.3)
- Inform patients, caregivers and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician. (5.3)
- Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation. (5.3)
- XENAZINE is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression. (4, 5.3)

INDICATIONS AND USAGE

XENAZINE is a vesicular monoamine transporter 2 (VMAT) inhibitor indicated for the treatment of chorea associated with Huntington's disease. (1)

DOSAGE AND ADMINISTRATION

- Individualization of dose with careful weekly titration is required. The 1st week's starting dose is 12.5 mg daily; 2nd week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose that reduces chorea. (2.1, 2.2)
- Doses of 37.5 mg and up to 50 mg per day should be administered in three divided doses per day with the maximum recommended single dose not to exceed 25 mg. (2.2)
- Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM). (2.2, 5.4)

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WARNING: DEPRESSION AND SUICIDALITY

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- Controlled Substance
- Abuse

- The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg. (2.2)
- The maximum daily dose in EMs and intermediate metabolizers (IMs) 100 mg with a maximum single dose of 37.5 mg. (2.2)
- If serious adverse events occur, titration should be stopped and the dose of XENAZINE should be reduced. If the adverse event(s) do not resolve, consider withdrawal of XENAZINE. (2.2, 5.2)

DOSAGE FORMS AND STRENGTHS

- 12.5 mg and 25 mg XENAZINE tablets for oral use (12.5 mg non-scored, 25 mg scored). (3)

CONTRAINDICATIONS

- XENAZINE is contraindicated in patients who are actively suicidal, or who have depression which is untreated or undertreated. (4, 5.3)
- XENAZINE is contraindicated in patients with impaired hepatic function. (2.4, 4, 8.6, 12.3)
- XENAZINE is contraindicated in patients taking MAOIs or reserpine. (4, 7.3, 7.4)

WARNINGS AND PRECAUTIONS

- Periodically reevaluate the benefit of XENAZINE and potential for adverse effects such as worsening mood, cognition, rigidity and functional capacity. (5.1)
- Do not exceed 50 mg/day and the maximum single dose should not exceed 25 mg if administered in conjunction with a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine). (5.3, 7.1)
- Neuroleptic Malignant Syndrome (NMS). (5.5, 7.6) Discontinue XENAZINE if this occurs. (5.5, 7.6)
- Restlessness, agitation, akathisia and parkinsonism. Reduce dose or discontinue XENAZINE if this occurs. (5.6, 5.7)
- Dysphagia and aspiration pneumonia. Monitor for dysphagia. (5.8)
- Sedation/somnolence. May impair the patient's ability to drive or operate complex machinery. (5.9)
- Alcohol or other sedating drugs can worsen sedation and somnolence. (5.10, 7.4)
- QTc prolongation. Do not prescribe in combination with other drugs that prolong QTc. (5.11, 7.5, 7.6, 12.2)
- Exaggerates extrapyramidal disorders when used with drugs that reduce or antagonize dopamine. Discontinue XENAZINE if this occurs. (5.15)

ADVERSE REACTIONS

The most common adverse reactions are (>10% and at least 5% greater than placebo): Sedation/somnolence, fatigue, insomnia, depression, akathisia, anxiety, nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact XENAZINE Information Center at 1-888-882-6013 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, tetrabenazine may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide

Revised: 05/2011

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* Sections or subsections omitted from the full prescribing information are not listed.

2.5 Discontinuation of Treatment

Treatment with XENAZINE can be discontinued without tapering. Re-emergence of chorea may occur within 12 to 18 hours after the last dose of XENAZINE. [see *Drug Abuse and Dependence* (9.2)].

2.6 Resumption of Treatment

Following treatment interruption of greater than five (5) days, XENAZINE therapy should be re-titrated when resumed. For short-term treatment interruption of less than five (5) days, treatment can be resumed at the previous maintenance dose without titration.

3 DOSAGE FORMS AND STRENGTHS

XENAZINE tablets are available in the following strengths and packages:

The 12.5 mg XENAZINE tablets are white, cylindrical biphasic tablets with beveled edges, non-scored, embossed on one side with "CL" and "12.5." The 25 mg XENAZINE tablets are yellowish-buff, cylindrical biphasic tablets with beveled edges, scored, embossed on one side with "CL" and "25."

4 CONTRAINDICATIONS

- XENAZINE is contraindicated in patients who are actively suicidal, or in patients with untreated or inadequately treated depression [see *Warnings and Precautions* (5.3)].
- XENAZINE is contraindicated in patients with impaired hepatic function. [see *Dosage and Administration* (2.4), *Warnings and Precautions* (5.16), *Use in Specific Populations* (8.6), and *Clinical Pharmacology* (12.3)].
- XENAZINE is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. [see *Warnings and Precautions* (5.12) and *Drug Interactions* (7.2, 7.3)].
- XENAZINE is contraindicated in patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting XENAZINE. [see *Warnings and Precautions* (5.12) and *Drug Interactions* (7.2)].

5 WARNINGS AND PRECAUTIONS

5.1 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, 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. Therefore, proper use of the drug requires attention to all facets of the underlying disease process over time.

Prescribers should periodically re-evaluate the need for XENAZINE in their patients by assessing the beneficial effect on chorea and possible adverse effects, including depression, cognitive decline, parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness and disability. It may be difficult to distinguish between drug-induced side-effects and progression of the underlying disease, decreasing the dose or stopping the drug may help the clinician distinguish between the two possibilities. In some patients, underlying chorea itself may improve over time, decreasing the need for XENAZINE.

5.2 Dosing of XENAZINE

Proper dosing of XENAZINE involves titration of therapy to determine an individualized dose for each patient. When first prescribed, XENAZINE therapy should be titrated slowly over several weeks to allow the identification of a dose that both reduces chorea and is tolerated. [see *Dosage and Administration* (2.1)]. Some adverse effects such as depression, fatigue, insomnia, sedation/somnolence, parkinsonism and akathisia may be dose-dependent and may resolve or lessen with dosage adjustment or specific treatment. If the adverse effect does not resolve or decrease, consider discontinuing XENAZINE.

Doses above 50 mg should not be given without CYP2D6 genotyping patients to determine if they are poor metabolizers [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.8), and *Clinical Pharmacology* (12.3)].

5.3 Risk of Depression and Suicidality

Patients with Huntington's disease are at increased risk for depression, suicidal ideation or behaviors (suicidality). XENAZINE increases the risk for suicidality in patients with HD. All patients treated with XENAZINE should be observed for new or worsening depression or suicidality. If depression or suicidality does not resolve, consider discontinuing treatment with XENAZINE.

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 XENAZINE were reported to have an adverse event of depression or worsening depression compared to none of the 30 placebo-treated patients. In two open-label studies (in one study, 29 patients received XENAZINE for up to 48 weeks; in the second study, 75 patients received XENAZINE for up to 80 weeks), the rate of depression/worsening depression was 35%.

In all of the HD chorea studies of XENAZINE (n=187), one patient committed suicide, one attempted suicide, and six had suicidal ideation. Clinicians should be alert to the heightened risk of suicide in patients with Huntington's disease regardless of depression indices. Reported rates of completed suicide among individuals with Huntington's disease range from 3-13% and over 25% of patients attempt suicide at some point in their illness.

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

5.4 Laboratory Tests

Before prescribing a daily dose of XENAZINE that is greater than 50 mg per day, patients should be genotyped to determine if they express the drug metabolizing enzyme, CYP2D6. CYP2D6 testing is necessary to determine whether patients are poor metabolizers (PMs), extensive (EMs) or intermediate metabolizers (IMs) of XENAZINE.

Patients who are PMs of XENAZINE will have substantially higher levels of the primary drug metabolites (about 3-fold for α -HTBZ and 9-fold for β -HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient's CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 50 mg and the maximum recommended single dose is 25 mg [see *Dosage and Administration* (2.2), *Use in Specific Populations* (8.8), and *Clinical Pharmacology* (12.3)].

5.5 Risk of Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with XENAZINE and other drugs that reduce dopaminergic transmission [see *Warnings and Precautions* (5.12) and *Drug Interactions* (7.7)]. Clinical manifestations of NMS are hyperreflexia, 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 creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated; other serious medical illness (e.g., pneumonia, systemic infection), and untreated or inadequately treated extrapyramidal disorders can present with similar signs and symptoms. 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 XENAZINE and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

Recurrence of NMS has been reported. If treatment with XENAZINE is needed after recovery from NMS, patients should be monitored for signs of recurrence.

5.6 Risk of 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 XENAZINE-treated patients and 0% of placebo-treated patients. In an 80-week open-label study, akathisia was observed in 20% of XENAZINE-treated patients. Akathisia was not observed in a 48-week open-label study. Patients receiving XENAZINE should be monitored for the presence of akathisia. Patients receiving XENAZINE 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 XENAZINE dose should be reduced; however, some patients may require discontinuation of therapy.

5.7 Risk of Parkinsonism

XENAZINE can cause parkinsonism. In a 12-week double-blind, placebo-controlled study in patients with chorea associated with HD, symptoms suggestive of parkinsonism (i.e., bradykinesia, hypotonia and rigidity) were observed in 15% of XENAZINE-treated patients compared to 0% of placebo-treated patients. In 48-week and 80-week open-label studies, symptoms suggestive of parkinsonism were observed in 10% and 3% of XENAZINE-treated patients, respectively. Because rigidity can develop as part of the underlying disease process in Huntington's disease, it may be difficult to distinguish between this drug-induced side-effect 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 Huntington's disease. If a patient develops parkinsonism during treatment with XENAZINE, dose reduction should be considered; in some patients, discontinuation of therapy may be necessary.

5.8 Risk of 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. In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with HD, dysphagia was observed in 4% of XENAZINE-treated patients and 3% of placebo-treated patients. In 48-week and 80-week open-label studies, dysphagia was observed in 10% and 5% of XENAZINE-treated patients, respectively. Some of the cases of dysphagia were associated with aspiration pneumonia. Whether these events were related to treatment is unknown.

5.9 Risk of Sedation and Somnolence

Sedation is the most common dose-limiting adverse effect of XENAZINE. In a 12-week, double-blind, placebo-controlled trial in patients with chorea associated with HD, sedation/somnolence was observed in 17/54 (31%) XENAZINE-treated patients and in 1 (3%) placebo-treated patient. Sedation was the reason upward titration of XENAZINE was stopped and/or the dose of XENAZINE was decreased in 15/54 (28%) patients. In all but one case, decreasing the dose of XENAZINE resulted in decreased sedation. In 48-week and 80-week open-label studies, sedation/somnolence was observed in 17% and 57% of XENAZINE-treated patients, respectively. In some patients, sedation occurred at doses that were lower than recommended doses.

Patients should not perform activities requiring mental alertness to maintain the safety of themselves or others, such as operating a motor vehicle or operating hazardous machinery, until they are on a maintenance dose of XENAZINE and know how the drug affects them.

5.10 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. [see *Warnings and Precautions* (5.9) and *Drug Interactions* (7.3)].

5.11 Risk of QTc Prolongation

XENAZINE causes a small increase (about 8 msec) in the corrected QT (QTc) interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases. [see *Clinical Pharmacology* (12.2)]. The use

of XENAZINE should be avoided in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval. [see *Drug Interactions* (7.5, 7.6) and *Use in Specific Populations* (8.10)].

XENAZINE should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may also increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval. [see *Use in Specific Populations* (8.10)].

5.12 Concomitant Use of Neuroleptic Drugs, Reserpine and MAOIs

Neuroleptic Drugs

Patients taking neuroleptic (antipsychotic) drugs (e.g., chlorpromazine, haloperidol, olanzapine, risperidone, 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. [see *Warnings and Precautions* (5.5, 5.11), *Drug Interactions* (7.5, 7.6) and *Use in Specific Populations* (8.10)].

Reserpine

Reserpine binds irreversibly to VMAT2, and the duration of its effect is several days. The physician should wait for chorea to remerge before administering XENAZINE to avoid overdosage and major depletion of serotonin and norepinephrine in the CNS. At least 20 days should elapse after stopping reserpine before starting XENAZINE. XENAZINE and reserpine should not be used concomitantly. [see *Contraindications* (4) and *Drug Interactions* (7.2)].

Monoamine Oxidase Inhibitors (MAOIs)

XENAZINE is contraindicated in patients taking MAOIs. XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. [see *Contraindications* (4) and *Drug Interactions* (7.3)].

5.13 Risk of Hypotension and Orthostatic Hypotension

XENAZINE induced postural dizziness in healthy volunteers receiving single doses of 25 or 50 mg. One subject had syncope and one subject with postural dizziness had documented orthostasis. Dizziness occurred in 4% of XENAZINE-treated patients (vs. none on placebo) in the 12-week controlled trial; however, blood pressure was not measured during these events. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension.

5.14 Risk of Hyperprolactinemia

XENAZINE elevates serum prolactin concentrations in humans. Following administration of 25 mg to healthy volunteers, peak plasma prolactin levels increased 4- to 5-fold. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance. XENAZINE is being considered for a patient with previously detected breast cancer. Although amenorrhea, galactorrhea, gynecostasia 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 (although not evaluated in the XENAZINE development program) has been associated with low levels of estrogen and increased risk of osteoporosis. If there is a clinical suspicion of symptomatic hyperprolactinemia, appropriate laboratory testing should be done and consideration should be given to discontinuation of XENAZINE.

5.15 Risk of Tardive Dyskinesia (TD)

A potentially irreversible syndrome of involuntary dyskinetic movements may develop in patients treated with neuroleptic drugs. In an animal model of orofacial dyskinesias, acute administration of reserpine, a monoamine depletor, has been shown to produce vacuous chewing in rats. Although the pathophysiology of tardive dyskinesia remains incompletely understood, the most commonly accepted hypothesis of the mechanism is that prolonged post-synaptic dopamine receptor blockade leads to supersensitivity to dopamine. Neither reserpine nor XENAZINE, which are dopamine depletors, have been reported to cause clear tardive dyskinesia in humans, but as pre-synaptic dopaminergic depletor could theoretically lead to supersensitivity to dopamine, and XENAZINE can cause the extrapyramidal symptoms also known to be associated with neuroleptics (e.g., parkinsonism and akathisia), physicians should be aware of the possible risk of tardive dyskinesia. If signs and symptoms of TD appear in a patient treated with XENAZINE, drug discontinuation should be considered.

5.16 Use in Patients with Concomitant Illnesses

Clinical experience with XENAZINE in patients with systemic illnesses is limited.

Depression and Suicidality

XENAZINE may increase the risk for depression or suicidality in patients with a history of depression or suicidal behavior or in patients with diseases, conditions, or treatments that cause depression or suicidality. XENAZINE is contraindicated in patients with untreated or inadequately treated depression or who are actively suicidal. [see *Contraindications* (4), *Warnings and Precautions* (5.3), and *Use in Specific Populations* (8.7)].

Hepatic Disease

XENAZINE is contraindicated in patients with hepatic impairment. [see *Dosage and Administration* (2.4), *Contraindications* (4), *Use in Specific Populations* (8.6), and *Clinical Pharmacology* (12.3)].

Heart Disease

XENAZINE has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials.

5.17 Binding to Melanin-Containing Tissues

Since XENAZINE or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that XENAZINE may cause toxicity in these tissues after extended use. Neither ophthalmologic nor microscopic examination of the eye was conducted in the chronic toxicity study in dogs. Ophthalmologic monitoring in humans was inadequate to exclude the possibility of injury occurring after long-term exposure.

The clinical relevance of XENAZINE's binding to melanin-containing tissues is unknown. Although there are no specific recommendations for periodic ophthalmologic monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects. [see *Clinical Pharmacology* (12.2)].

6 ADVERSE REACTIONS

The following risks are discussed in greater detail in other sections of the labeling:

- Depression and suicidality [see *Warnings and Precautions* (5.3)]
- Akathisia, restlessness and agitation [see *Warnings and Precautions* (5.6)]
- Parkinsonism [see *Warnings and Precautions* (5.7)]
- Sedation and somnolence [see *Warnings and Precautions* (5.9)]
- Dysphagia [see *Warnings and Precautions* (5.8)]

6.1 Commonly Observed Adverse Reactions in Controlled Clinical Trials

The most common adverse reactions from Table 1 occurring in over 10% of XENAZINE-treated patients, and at least 5% greater than placebo, were sedation/somnolence (31%), fatigue (22%), insomnia (22%), depression (19%), akathisia (19%), and nausea (13%).

6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly

Body System	AE Term	XENAZINE n = 54 n (%)	Placebo n = 30 n (%)
GASTROINTESTINAL SYSTEM DISORDERS	Nausea	7 (13%)	2 (7%)
	Vomiting	3 (6%)	1 (3%)
	Fatigue	12 (22%)	4 (13%)
BODY AS A WHOLE – GENERAL	Fall	8 (15%)	4 (13%)
	Laceration (head)	3 (6%)	-
	Echymosis	3 (6%)	-
	Upper respiratory tract infection	6 (11%)	2 (7%)
RESPIRATORY SYSTEM DISORDERS	Shortness of breath	2 (4%)	-
	Bronchitis	2 (4%)	-
	Dysuria	2 (4%)	-

Dose escalation was discontinued or dosage of study drug was reduced because of one or more AEs in 28 of 54 (52%) patients randomized to XENAZINE. These AEs consisted of sedation (15), akathisia (7), parkinsonism (4), depression (3), anxiety (2), fatigue (1) and diarrhea (1). Some patients had more than one AE and are, therefore, counted more than once.

Adverse Reactions Due to Extrapyramidal Symptoms (EPS)

The following table describes the incidence of events considered to be extrapyramidal adverse reactions.

Table 2. Treatment Emergent EPS in Patients Treated with XENAZINE occurring with a Greater Frequency than Placebo in the 12-Week, Double-Blind, Placebo-Controlled Trial of XENAZINE

Event	Patients (%) reporting event	
	XENAZINE n = 54	Placebo n = 30
Akathisia ¹	10 (19%)	0
Extrapyramidal event ²	8 (15%)	0
Any extrapyramidal event	18 (33%)	0

¹ Patients with the following adverse event preferred terms were counted in this category: akathisia, hyperkinesia, restlessness.

² Patients with the following adverse event preferred terms were counted in this category: bradykinesia, parkinsonism, extrapyramidal disorder, hypotonia.

Patients may have had events in more than one category.

6.3 Laboratory Tests

No clinically significant changes in laboratory parameters were reported in clinical trials with XENAZINE. In controlled clinical trials, XENAZINE caused a small mean increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), laboratory values as compared to placebo.

6.4 Vital Signs

In controlled clinical trials, XENAZINE did not affect blood pressure, pulse, and body weight. Orthostatic blood pressure was not consistently measured in the XENAZINE clinical trials.

7 DRUG INTERACTIONS

7.1 Strong CYP2D6 Inhibitors

In vitro studies indicate that α -HTBZ and β -HTBZ are substrates for CYP2D6. Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) markedly increase exposure to these metabolites. A reduction in XENAZINE dose may be necessary when adding a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine, quinidine) in patients maintained on a stable dose of XENAZINE. The daily dose of XENAZINE should not exceed 50 mg per day and the maximum single dose of XENAZINE should not exceed 25 mg in patient taking strong CYP2D6 inhibitors [see Dosage and Administration (2.2), Warnings and Precautions (5.3), Use in Specific Populations (8.9), and Clinical Pharmacology (12.3)].

7.2 Reserpine

Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Prescribers should wait for chorea to reemerge before administering XENAZINE to avoid overdosage and motor depletion of serotonin and norepinephrine in the CNS. At least 20 days should elapse after stopping reserpine before starting XENAZINE. XENAZINE and reserpine should not be used concomitantly [see Contraindications (4), Warnings and Precautions (5.12), and Clinical Pharmacology (12.3)].

7.3 Monoamine Oxidase Inhibitors (MAOIs)

XENAZINE is contraindicated in patients taking MAOIs. XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI [see Contraindications (4), Warnings and Precautions (5.12), and Clinical Pharmacology (12.3)].

7.4 Alcohol

Concomitant use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence [see Warnings and Precautions (5.10)].

7.5 Drugs that Cause QTc Prolongation

Since XENAZINE causes a small increase in QTc prolongation (about 8 msec), the concomitant use with other drugs that are known to cause QTc prolongation should be avoided including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval. XENAZINE should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval [see Warnings and Precautions (5.11, 5.12), Drug Interactions (7.7), and Clinical Pharmacology (12.2)].

7.6 Neuroleptic Drugs

Adverse reactions associated with XENAZINE, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists, including antipsychotics (e.g., chlorpromazine, haloperidol, olanzapine, risperidone, thioridazine, ziprasidone) [see Warnings and Precautions (5.5, 5.10, 5.11, 5.12) and Drug Interactions (7.6)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. XENAZINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Tetrazepam 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). Tetrazepam 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/m² basis). Because neither rat nor rabbit dosed with tetrazepam produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately addressed the potential effects of tetrazepam on embryo-fetal development in humans.

When tetrazepam 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/m² basis. Because rats dosed with tetrazepam do not produce 9-desmethyl-beta-DHTBZ, a major human metabolite, this study may not have adequately assessed the potential effects of tetrazepam on the offspring of women exposed *in utero* and via lactation.

8.2 Labor and Delivery

The effect of XENAZINE on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether XENAZINE or its metabolites are excreted in human milk.

Since many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from XENAZINE, a decision should be made whether to discontinue nursing or to discontinue XENAZINE, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of XENAZINE in children have not been established.

8.5 Geriatric Use

The pharmacokinetics of XENAZINE and its primary metabolites have not been formally studied in geriatric subjects.

8.6 Use in Patients with Hepatic Disease

The use of XENAZINE in patients with liver disease is contraindicated [see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.16), and Clinical Pharmacology (12.3)].

8.7 Use in Patients with Depression and Suicidality

Patients with HD are at increased risk for depression, suicidal ideation and behavior (suicidality), and XENAZINE increases these risks. XENAZINE is contraindicated in patients with untreated or inadequately treated depression or who are actively suicidal. XENAZINE may increase the risk for depression or suicidality in patients with a history of depression or suicidal behavior or in patients with diseases, conditions, or treatments that cause depression or suicidality [see Contraindications (4) and Warnings and Precautions (5.3)].

Depression

Symptoms of sadness, worsening of depression, withdrawal, insomnia, irritability, hostility (aggressiveness), akathisia (psychomotor restlessness), anxiety, agitation, or panic attacks may increase with XENAZINE. Depression/worsening depression was noted in 35% of XENAZINE-treated patients during studies with XENAZINE.

Suicidality

The rate of completed suicide among individuals with Huntington's disease ranges from 3-13% and over 25% of patients with HD attempt suicide at some point in their illness.

8.8 Use in Poor or Extensive CYP2D6 Metabolizers

Patients who require doses of XENAZINE greater than 50 mg per day, should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized according to their status as either poor (PMs) or extensive metabolizers (EMs) [see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.4) and Clinical Pharmacology (12.3)].

Poor Metabolizers

Poor CYP2D6 metabolizers (PM) will have substantially higher levels of exposure to the primary metabolites (about 3-fold for α -HTBZ and 9-fold for β -HTBZ) compared to EMs. The dosage should, therefore, be adjusted according to a patient's CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose to not exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs [see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.4), and Clinical Pharmacology (12.3)].

Extensive/Intermediate Metabolizers

In extensive (EMs) or intermediate metabolizers (IMs), the dosage of XENAZINE can be titrated to a maximum single dose of 37.5 mg and a recommended maximum daily dose of 100 mg [see Dosage and Administration (2.2), Drug Interaction (7.1), and Clinical Pharmacology (12.3)].

8.9 Use in Patients at Risk from QTc Prolongation

XENAZINE causes a small increase in QTc interval (8 msec). It should be avoided in patients with congenital long QT syndrome, or a history of hypokalemia or hypomagnesemia, or cardiac arrhythmias (e.g., bradycardia), or in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval [see Warnings and Precautions (5.5, 5.11, 5.12), Drug Interactions (7.5, 7.6), and Clinical Pharmacology (12.2)].

8.10 Use in Patients with Renal Disease

The effects of renal insufficiency in the pharmacokinetics of XENAZINE and its primary metabolites have not been formally studied.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Class

XENAZINE is not a controlled substance.

9.2 Abuse

Clinical trials did not reveal any tendency for drug seeking behavior, though these observations were not systematic. Abuse has not been reported from the postmarketing experience in countries where XENAZINE has been marketed.

As with any CNS-active drug, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of XENAZINE misuse or abuse (such as development of tolerance, increasing dose requirements, drug-seeking behavior).

Abrupt discontinuation of XENAZINE from patients did not produce symptoms of withdrawal or a discontinuation syndrome; only symptoms of the original disease were observed to re-emerge [see Dosage and Administration (2.5)].

10 OVERDOSAGE

10.1 Human Experience

Three episodes of overdose occurred in the open-label trials performed in support of registration. Eight cases of overdose with XENAZINE have been reported in the literature. The dose of XENAZINE in these patients ranged from 100 mg to 1g. Adverse reactions associated with XENAZINE overdose included acute dystonia, oculogyric crisis, nausea and vomiting, sweating, sedation, hypotension, confusion, diarrhea, hallucinations, rubor, and tremor.

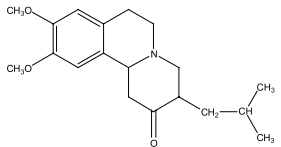
10.2 Management of Overdose

Treatment should consist of those general measures employed in the management of overdose with any CNS-active drug. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital signs should be monitored. In managing overdose, the possibility of multiple drug involvement should always be considered. The physician should consider contacting a poison control center on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR®).

11 DESCRIPTION

XENAZINE (tetrazepam) is a monoamine depletor for oral administration. The molecular weight of tetrazepam is 317.43; the pKa is 6.51. Tetrazepam is a hexahydro-dimethyl benzopyridine derivative and has the following chemical name: cis rac -1,3,4,6,7,11-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[quinolin]-2-one.

The empirical formula C₂₁H₂₇NO₃ is represented by the following structural formula:



Tetrazepam is a white to slightly yellow crystalline powder that is sparingly soluble in water and soluble in ethanol.

Each XENAZINE (tetrazepam) Tablet contains either 12.5 or 25 mg of tetrazepam as the active ingredient. XENAZINE (tetrazepam) Tablets contain tetrazepam as the active ingredient and the following inactive ingredients: lactose, magnesium stearate, maize starch, and talc. The 25 mg strength tablet also contains yellow iron oxide as an inactive ingredient. XENAZINE (tetrazepam) is supplied as a yellowish-buff scored tablet containing 25 mg of XENAZINE or as a white non-scored tablet containing 12.5 mg of XENAZINE.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which XENAZINE (tetrazepam) exerts its anti-chorea effects is unknown but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. Tetrazepam reversibly inhibits the human vesicular monoamine transporter type 2 (VMAT2) (K_i = 100 nM), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. Human VMAT2 is also inhibited by dihydropyridine (HTBZ), a mixture of α -HTBZ and β -HTBZ. α - and β -HTBZ, major circulating metabolites in humans, exhibit high *in vitro* binding affinity to bovine VMAT2. Tetrazepam exhibits weak *in vitro* binding affinity at the dopamine D2 receptor (K_i = 2100 nM).

12.2 Pharmacodynamics

QTc Prolongation

The effect of a single 25 or 50 mg dose of XENAZINE on the QT interval was studied in a randomized, double-blind, placebo controlled crossover study in healthy male and female subjects with moxifloxacin as a positive control. At 50 mg, XENAZINE caused an approximately 8 msec mean increase in QTc (90% CI: 5.0, 10.4 msec). Additional data suggest that inhibition of CYP2D6 in healthy subjects given a single 50 mg dose of XENAZINE does not further increase the effect on the QTc interval. Effects at higher exposures to either XENAZINE or its metabolites have not been evaluated [see Warnings and Precautions (5.11, 5.12), Drug Interactions (7.6, 7.7), and Use in Specific Populations (8.10)].

Melanin Binding

Tetrazepam and its metabolites bind to melanin-containing tissues (i.e., eye, skin, fur) in pigmented rats. After a single oral dose of radiolabeled tetrazepam, radioactivity was still detected in eye and fur at 21 days post dosing [see Warnings and Precautions (5.17)].

12.3 Pharmacokinetics

Absorption

Following oral administration of tetrazepam, the extent of absorption is at least 75%. After single oral doses ranging from 12.5 to 50 mg, plasma concentrations of tetrazepam are generally below the limit of detection because of the rapid and extensive hepatic metabolism of tetrazepam by carbonyl reductase to the active metabolites α -HTBZ and β -HTBZ. α -HTBZ and β -HTBZ are metabolized principally by CYP2D6. Peak plasma concentrations (C_{max}) of α -HTBZ and β -HTBZ are reached within 1 to 1½ hours post-dosing. α -HTBZ is subsequently metabolized to a minor metabolite, 9-desmethyl- α -DHTBZ. β -HTBZ is subsequently metabolized to another major circulating metabolite, 9-desmethyl- β -DHTBZ, for which C_{max} is reached approximately 2 hours post-dosing.

Food Effects

The effects of food on the bioavailability of XENAZINE were studied in subjects administered a single dose with and without food. Food had no effect on mean plasma concentrations, C_{max}, or the area under the concentration time course (AUC) of α -HTBZ or β -HTBZ. XENAZINE can, therefore, be administered without regard to meals.

Distribution

Results of PET-scan studies in humans show that radioactivity is rapidly distributed to the brain following intravenous injection of ¹¹C-labeled tetrazepam or α -HTBZ, with the highest binding in the striatum and lowest binding in the cortex.

The *in vitro* protein binding of tetrazepam, α -HTBZ, and β -HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrazepam binding ranged from 82% to 85%, α -HTBZ binding ranged from 60% to 68%, and β -HTBZ binding ranged from 59% to 63%.

Metabolism

After oral administration in humans, at least 19 metabolites of tetrazepam have been identified. α -HTBZ, β -HTBZ and 9-desmethyl- β -DHTBZ are the major circulating metabolites, and they are, subsequently, metabolized to sulfate or glucuronide conjugates. α -HTBZ and β -HTBZ are formed by carbonyl reductase that occurs mainly in the liver. α -HTBZ is O-dealkylated by CYP450 enzymes, principally CYP2D6, with some contribution of CYP1A2 to form 9-desmethyl- α -DHTBZ, a minor metabolite. β -HTBZ is O-dealkylated principally by CYP2D6 to form 9-desmethyl- β -DHTBZ.

The results of *in vitro* studies do not suggest that tetrazepam, α -HTBZ, or β -HTBZ are likely to result in clinically significant inhibition of CYP2D6, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. *In vitro* studies suggest that neither tetrazepam nor its α - or β -HTBZ metabolites are likely to result in clinically significant induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19. Neither tetrazepam nor its α - or β -HTBZ metabolites is likely to be a substrate or inhibitor of P-glycoprotein at clinically relevant concentrations *in vivo*.

No *in vitro* metabolism studies have been conducted to evaluate the potential of the 9-desmethyl- β -DHTBZ metabolite to interact with other drugs. The activity of this metabolite relative to the parent drug is unknown.

Elimination

After oral administration, tetrazepam is extensively hepatically metabolized, and the metabolites are primarily renally eliminated. α -HTBZ, β -HTBZ and 9-desmethyl- β -DHTBZ have half-lives of 7 hours, 5 hours and 12 hours respectively. In a mass balance study in 6 healthy volunteers, approximately 75% of the dose was excreted in the urine and fecal recovery accounted for approximately 7-16% of the dose. Unchanged tetrazepam has not been found in human urine. Urinary excretion of α -HTBZ or β -HTBZ accounted for less than 10% of the administered dose. Circulating metabolites, including sulfate and glucuronide conjugates of HTBZ metabolites as well as products of oxidative metabolism, account for the majority of metabolites in the urine.

Specific Populations

Pediatric Patient

The pharmacokinetics of XENAZINE and its primary metabolites have not been studied in pediatric subjects [see Use in Specific Populations (8.4)].

Geriatric Patient

The pharmacokinetics of XENAZINE and its primary metabolites have not been formally studied in geriatric subjects [see Use in Specific Populations (8.5)].

Gender

There is no apparent effect of gender on the pharmacokinetics of α -HTBZ or β -HTBZ.

Race

Racial differences in the pharmacokinetics of XENAZINE and its primary metabolites have not been formally studied.

Patients with Renal Impairment

The effect of renal insufficiency on the pharmacokinetics of XENAZINE and its primary metabolites has not been studied.

Patients with Hepatic Impairment

The disposition of tetrazepam was compared in 12 patients with mild to moderate chronic liver impairment (Child-Pugh scores of 5-9) and 12 age- and gender-matched subjects with normal hepatic function who received a single 25 mg dose of tetrazepam. In patients with hepatic impairment, tetrazepam plasma concentrations were similar to or higher than concentrations of α -HTBZ, reflecting the markedly decreased metabolism of tetrazepam to α -HTBZ. The mean tetrazepam C_{max} in hepatically impaired subjects was approximately 7- to 190-fold higher than the detectable peak concentrations in healthy subjects. The elimination half-life of tetrazepam in subjects with hepatic impairment was approximately 17.5 hours. The time to peak concentrations (t_{max}) of α -HTBZ and β -HTBZ was slightly delayed in subjects with hepatic impairment compared to age-matched controls (1.75 hrs vs. 1.0 hrs), and the elimination half lives of the α -HTBZ and β -HTBZ were prolonged to approximately 10 and 8 hours, respectively. The exposure to α -HTBZ and β -HTBZ was approximately 30-35% greater in patients with liver impairment than in age-matched controls. The safety and efficacy of this increased exposure to tetrazepam and other circulating metabolites are unknown so that it is not possible to adjust the dosage of tetrazepam in hepatic impairment to ensure safe use. Therefore, tetrazepam is contraindicated in patients with hepatic impairment [see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.16), and Use in Specific Populations (8.6)].

Patients Who Are Poor or Extensive CYP2D6 Metabolizers

Patients should be genotyped for drug metabolizing enzyme, CYP2D6, prior to treatment with daily doses of XENAZINE over 50 mg [see Dosage and Administration (2.2), Warnings and Precautions (5.4), and Use in Specific Populations (8.8)].

Poor Metabolizers

Although the pharmacokinetics of XENAZINE and its metabolites in subjects who do not express the drug metabolizing enzyme, CYP2D6, poor metabolizers, (PMs), have not been systematically evaluated, it is likely that the exposure to α -HTBZ and β -HTBZ would be increased similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively). Patients who are PMs should not be given doses greater than 50 mg per day and the maximum recommended single dose is 25 mg [see Dosage and Administration (2.2), Warnings and Precautions (5.3, 5.4), and Use in Specific Populations (8.8)].

Extensive or Intermediate CYP2D6 Metabolizers

In patients who express the enzyme, CYP2D6, (extensive [EMs] or intermediate [IMs] metabolizers), the maximum recommended daily dose is 100 mg per day, with a maximum recommended single dose of 37.5 mg [see Dosage and Administration (2.2), Warnings and Precautions (5.4), and Use in Specific Populations (8.8)].

Drug Interactions

CYP2D6 Inhibitors

In vitro studies indicate that α -HTBZ and β -HTBZ are substrates for CYP2D6. The effect of CYP2D6 inhibition on the pharmacokinetics of tetrazepam and its metabolites was studied in 25 healthy subjects following a single 50 mg dose of tetrazepam given after 10 days of administration of the strong CYP2D6 inhibitor paroxetine 20 mg daily. There was an approximately 30% increase in C_{max} and an approximately 3-fold increase in AUC for α -HTBZ in subjects given paroxetine prior to tetrazepam compared to tetrazepam given alone. For β -HTBZ, the C_{max} and AUC were increased 2.4- and 9-fold, respectively, in subjects given paroxetine prior to tetrazepam given alone. The elimination half-life of α -HTBZ and β -HTBZ was approximately 14 hours when tetrazepam was given with paroxetine. Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) markedly increase exposure to these metabolites. The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline on the exposure to XENAZINE and its metabolites has not been evaluated [see Dosage and Administration (2.3), Warnings and Precautions (5.3), Drug Interactions (7.1), and Use in Specific Populations (8.9)].

Digoxin

Digoxin is a substrate for P-glycoprotein. A study in healthy volunteers showed that XENAZINE (25 mg twice daily for 3 days) did not affect the bioavailability of digoxin, suggesting that at this dose, XENAZINE does not affect P-glycoprotein in the intestinal tract. *In vitro* studies also do not suggest that XENAZINE or its metabolites are P-glycoprotein inhibitors.

Reserpine

XENAZINE is contraindicated in patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting XENAZINE [see Contraindications (4), Warnings and Precautions (5.12), and Drug Interactions (7.3)].



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 **Xenazine**®
(tetrabenazine)
12.5 and 25 mg Tablets

The Xenazine logo features the word "Xenazine" in a bold, dark blue sans-serif font, with a registered trademark symbol. A green swoosh underline is positioned beneath the "Xenazine" text. Below this, the word "(tetrabenazine)" is written in a smaller, dark blue sans-serif font. At the bottom, the text "12.5 and 25 mg Tablets" is displayed in a small, dark blue sans-serif font.