Initial REMS Approval: 08/15/2008
Most Recent Modification: August 2013

NDA 21-894 Xenazine® (tetrabenazine)

Valeant Pharmaceuticals North America LLC
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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

The goal of the REMS for Xenazine is:

- To inform healthcare professionals of the increased risk of drug-associated depression and suicidality, proper titration and dosing, and the risk of drug-drug interactions with strong CYP2D6 inhibitors in patients taking Xenazine.

II. REMS ELEMENTS

A. Communication Plan

Valeant will implement a communication plan to healthcare providers to support implementation of this REMS:

1 The audience is healthcare professionals (HCPs) – especially neurologists and movement disorder specialists and pharmacists.
2 Valeant will provide physicians and pharmacists with the education materials listed below that describe the key risks and benefits of tetrabenazine:

a. Prescriber materials:
   i. Xenazine® Package Insert (PI)
   ii. Dear Healthcare Professional Letter
   iii. Xenazine® Medication Guide
   iv. Prescribing Xenazine® (tetrabenazine) Tablets: A Healthcare Professional Guide
   v. Patient/Caregiver Counseling Guide
   vi. Initial Dosing Plan
   vii. Xenazine Fact Sheet for Healthcare Professionals

b. Pharmacist materials
   i. Dear Pharmacist Letter
   ii. Xenazine® Package Insert (PI)
   iii. Xenazine® Medication Guide
   iv. Prescribing Xenazine® (tetrabenazine) Tablets: A Healthcare Professional Guide

c. All final communication and educational materials listed above are appended to the REMS.

3 Pharmacy Management Systems – Valeant will work with First Data Bank, MediSpan, Facts and Comparisons, Micromedex, major pharmacy benefit managers and other leading providers of point of sale clinical alert data to inform dispensing pharmacists and pharmacy technicians of the significant known risks of tetrabenazine. In working with these data providers, Valeant will seek to include appropriate drug-drug interaction information, dosing guidelines and other clinical alerts available to it through the use of standard NCPDP data formats.

4 Ongoing Healthcare Professional Education – The Sponsor will also use several educational vehicles to continue educating and updating Healthcare Professionals about tetrabenazine and the REMS. These include a trained Speaker's Bureau which will schedule local and regional thought leader symposia. The speaker materials will include information on the tetrabenazine REMS and will be used to reinforce the risk minimization measures after launch. The Sponsor's clinical team and sales professionals will be present at annual meetings of the major professional societies of neurologists and movement disorder specialists (e.g., American Academy of Neurology, American Neurological Association, Movement Disorder Society) and will use these opportunities to reinforce the REMS messages. Continuing education formats will also be available for physicians and pharmacists on the product web site.

5 Distribution of materials:

a. At the time of tetrabenazine availability, the Dear Healthcare Professional Letter will be sent by mass mailing to targeted medical specialists to announce the availability of tetrabenazine and to educate them on proper patient selection and use of the drug. The mailing will also include a copy of the PI, the *Prescribing Xenazine® (tetrabenazine) Tablets: A Healthcare Professional Guide*, the patient Medication Guide, the *Patient/Caregiver Counseling Guide* and the Initial Dosing Plan (as described above). Additional materials will be available via sales and/or clinical representatives, the product website or through the Sponsor toll-free medical information line.

b. At the time of tetrabenazine availability, a letter will be sent by mass

mailing to pharmacists who dispense tetrabenazine through specialty pharmacies to announce the availability of tetrabenazine and to educate pharmacists on the tetrabenazine REMS. The mailing will also include a copy of the PI and the *Prescribing Xenazine® (tetrabenazine) Tablets: A Healthcare Professional Guide*. Pharmacists will also be provided with 10 copies of the Medication Guide. The pharmacist can obtain additional educational materials from the Sponsor toll-free medical information line or the product website.

c. In order to ensure that healthcare professionals remain informed of the tetrabenazine REMS, the Dear Healthcare Professional letter and the Dear Pharmacist letter will be updated and distributed annually from the date of the initial approval of the REMS (August 15, 2008) and sent to all neurologists, movement disorder specialists and pharmacists within the specialty pharmacy networks authorized to dispense Xenazine. These annual mailings will include the most current *Prescribing Xenazine® (tetrabenazine) Tablets: A Healthcare Professional Guide, What You Need to Know About Xenazine®: Patient/Caregiver Counseling Guide*, and Medication Guide. The *Xenazine Fact Sheet for Healthcare Professionals*, which was created in May 2013, will be included with the final distribution of the Dear Healthcare Professional Letter. The final distribution date will be August 15, 2013.

B. Timetable for Submission of Assessments

Valeant will submit REMS Assessments to the FDA at 18 months, 3 years, 4 years, 6 years, and 7 years from the date of initial approval of the REMS (August 15, 2008). The 6 year assessment report will be limited to a prescriber survey designed to monitor prescriber understanding of the proper use of Xenazine therapy and compliance with the titration and dosing guidelines contained in the labeling. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Valeant will submit each assessment so that it will be received by the FDA on or before the due date.

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IMPORTANT DRUG WARNING

May 2013

Dear Healthcare Professional:

This letter serves to inform you of the Important Safety Information about Xenazine® (tetrabenazine) Tablets, indicated for the treatment of chorea associated with Huntington's disease, and to remind you of the educational materials that are available to prescribing healthcare professionals, patients, and caregivers.

Xenazine was approved by the Food and Drug Administration (FDA) in August 2008 with a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks.

SERIOUS RISKS ASSOCIATED WITH XENAZINE INVOLVE:

Drug-Associated Depression and Suicidality (Boxed Warning)

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.

Need for Proper Titration and Dosing

- The dose for Xenazine should be individualized. When first prescribed, Xenazine therapy should be initiated as 12.5 mg per day given once in the morning. The dose should be titrated slowly at weekly intervals by 12.5 mg to allow for the identification of a dose that reduces chorea and is tolerated.
- Patients must be carefully monitored during titration and continued therapy to detect treatment-emergent depression and suicidal behavior and other adverse events. The dose should be adjusted accordingly or discontinued.
- Patients requiring doses greater than 50 mg per day should be first tested and genotyped for the drug-metabolizing enzyme CYP2D6 to determine if the patient is a poor or extensive metabolizer. (See the enclosed Xenazine® (tetrabenazine) Fact Sheet for Healthcare Professionals for further information.)

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Drug–Drug Interactions With CYP2D6 Inhibitors

- Caution should be used when adding therapy with a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, quinidine) to patients already receiving a stable dose of Xenazine; a reduction in Xenazine dose may be necessary. (See the enclosed Xenazine® (tetrabenazine) Fact Sheet for Healthcare Professionals for further information.)
- 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 patients taking strong CYP2D6 inhibitors.

What to Discuss With Your Patients

Xenazine treatment should not be started before the patient has been counseled on the Important Safety Information. Patients should be reminded of the signs and symptoms of depression during each visit. The following materials are enclosed and available to your patients and their caregivers to help educate them on the benefits and risks of taking Xenazine:

- Xenazine Medication Guide
- *What You Need to Know About Xenazine® (tetrabenazine)*
- The Initial Dosing Plan

A copy of the Xenazine Medication Guide should be given to the patient prior to the initiation of treatment and with each refilled prescription. The healthcare professional should also distribute the Patient/Caregiver Counseling Guide, *What You Need to Know About Xenazine® (tetrabenazine),* which provides helpful information for the patient/caregiver on what to expect while on Xenazine. The Initial Dosing Plan should be filled in by the healthcare professional for each patient, as appropriate.

Copies of the following materials for healthcare professionals are also included with this letter:

- Xenazine Prescribing Information
- *Prescribing Xenazine® (tetrabenazine) Tablets: A Healthcare Professional Guide*
- Xenazine® (tetrabenazine) Fact Sheet for Healthcare Professionals

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Reporting Adverse Events

Adverse event information should be reported to the Xenazine Information Center at 1-888-882-6013.

You may also report adverse event information to the FDA MedWatch Reporting System by one of the following methods:

- Online at www.fda.gov/medwatch/report.htm
- Phone at 1-800-FDA-1088

Should you have questions concerning Xenazine product information or wish to request a visit from a Lundbeck sales representative, please call the Xenazine Information Center at 1-888-882-6013.

Sincerely,

Christopher Silber, MD
VP, US Clinical Development Center
Lundbeck

www.XenazineUSA.com

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May 2013

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- **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.**
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- **XENAZINE is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression.**

Need for Proper Titration and Dosing

- When first prescribed, Xenazine therapy should be initiated as 12.5 mg per day given once in the morning. The dose should be titrated slowly at weekly intervals by 12.5 mg to allow for the identification of a dose that reduces chorea and is tolerated.

Drug–Drug Interactions With CYP2D6 Inhibitors

- Caution should be used when adding therapy with a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine, 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.

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The FDA requires that a copy of the Xenazine Medication Guide be distributed to each patient who fills a prescription for Xenazine. Additional copies of the most current Xenazine Medication Guide are available by calling the Xenazine Information Center at 1-888-882-6013 or by accessing the Xenazine website at www.XenazineUSA.com.

The following documents are included to help you understand how Xenazine is prescribed and to answer questions posed by patients. You may also find these at www.XenazineUSA.com.

- Xenazine Prescribing Information
- 10 copies of the Xenazine Medication Guide
  - Tear pads of the Xenazine Medication Guide are also distributed with orders for your convenience
- *Prescribing Xenazine® (tetrabenazine) Tablets: A Healthcare Professional Guide* that outlines the Xenazine Important Safety Information, including the Xenazine REMS

Reporting Adverse Events

Adverse event information should be reported to the Xenazine Information Center at 1-888-882-6013.

You may also report adverse event information to the FDA MedWatch Reporting System by one of the following methods:

- Online at www.fda.gov/medwatch/report.htm
- Phone at 1-800-FDA-1088

Should you have questions concerning Xenazine product information or wish to request a visit from a Lundbeck sales representative, please call the Xenazine Information Center at 1-888-882-6013.

Sincerely,

Christopher Silber, MD
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XENAZINE® (TETRABENAZINE) FACT SHEET FOR HEALTHCARE PROFESSIONALS

Xenazine Metabolism and Testing for CYP2D6 Expression

- After oral administration in humans, Xenazine is extensively hepatically metabolized into several metabolites[1]
- The primary metabolites (α-d hydrotetrabenazine [HTBZ] and ß-HTBZ) are subsequently metabolized by CYP2D6[1]
- Poor CYP2D6 metabolizers will have substantially higher exposure to primary metabolites—approximately 3-fold for α-HTBZ and 9-fold for ß-HTBZ—compared with extensive metabolizers

Table 1. CYP2D6 Activity Based on Phenotype[2]

Phenotype	CYP2D6 Allele Expressed	CYP2D6 Activity	Implications
Poor Metabolizer (PM)	2 nonfunctional	None	Drug may not be metabolized rapidly enough, which can lead to accumulation and side effects
Intermediate Metabolizer (IM)	Usually 1 nonfunctional	Low	Response may be intermediate between PMs and EMs
Extensive Metabolizer (EM)	2 functional	Normal	Normal response to standard dosing
Ultrarapid Metabolizer (UM)*	≥3 functional	High	Drugs are metabolized too rapidly and standard dose may not have a therapeutic benefit

*Not included in Xenazine® (tetrabenazine) Prescribing Information.

Patients requiring doses >50 mg daily should be first tested and genotyped for CYP2D6 expression to determine metabolizer status.[1]

- The dose of Xenazine should be individualized according to a patient's CYP2D6 status[1]
  - The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg
  - The maximum daily dose in EMs and IMs is 100 mg with a maximum single dose of 37.5 mg
- 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.

Potential Drug Interactions With CYP2D6 Inhibitors

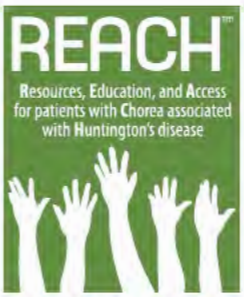
- Strong CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, quinidine) markedly increase exposure to α-HTBZ and ß-HTBZ; therefore, the total daily dose of Xenazine should not exceed a maximum of 50 mg and the maximum single dose should not exceed 25 mg[1]
- A reduction in Xenazine dose may be necessary when adding a strong CYP2D6 inhibitor in patients maintained on a stable dose of Xenazine

For more information, please see the accompanying Prescribing Information and Medication Guide.

References:
1. Xenazine [package insert]. Deerfield, IL: Lundbeck.
2. Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther.* 2007;116:496-526.

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 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.

Reference ID: 3351234

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.

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 population[1]; 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 times[2]:

- 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 Suicidality[3]

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.

Section V:

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.

Section VII:

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)
- 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: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Xenazine® (tetrabenazine) Tablets
FULL PRESCRIBING INFORMATION

WARNING: DEPRESSION AND SUICIDALITY

XENAZINE can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of XENAZINE must balance the risks of depression and suicidality with the clinical need for control of choreiform movements. Close observation of patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior should accompany therapy. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and should be instructed to report behaviors of concern promptly to the treating physician.

Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington's disease. XENAZINE is contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Considerations

The chronic daily dose of XENAZINE used to treat chorea associated with Huntington's disease (HD) is determined individually for each patient. When first prescribed, XENAZINE therapy should be titrated slowly over several weeks to identify a dose of XENAZINE that reduces chorea and is tolerated. XENAZINE can be administered without regard to food *[see Clinical Pharmacology (12.3)]*.

2.2 Individualization of Dose

The dose of XENAZINE should be individualized.

Dosing Recommendations Up to 50 mg per day

The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given as 12.5 mg twice a day. XENAZINE should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. If a dose of 37.5 to 50 mg per day is needed, it should be given in a three times a day regimen. The maximum recommended single dose is 25 mg. 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 (e.g., antidepressants) *[see Adverse Reactions (6.1)]*.

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

Dosing Recommendations Above 50 mg per day

Patients who require doses of XENAZINE greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized accordingly to their status as PMs or EMs *[see Warnings and Precautions (5.2, 5.4), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)]*.

Extensive and Intermediate CYP2D6 Metabolizers

Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of XENAZINE above 50 mg per day, should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. If adverse events such as akathisia, 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 (e.g., antidepressants) *[see Warnings and Precautions (5.2, 5.4), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)]*.

Poor CYP2D6 Metabolizers

In PMs, the initial dose and titration is similar to EMs except that the recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg *[see Warnings and Precautions (5.2), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)]*.

2.3 CYP2D6 Inhibitors

Strong CYP2D6 Inhibitors

Medications that are strong CYP2D6 inhibitors such as quinidine or antidepressants (e.g., fluoxetine, paroxetine) significantly increase the exposure to α-HTBZ and β-HTBZ, therefore, the total dose of XENAZINE should not exceed a maximum of 50 mg and the maximum single dose should not exceed 25 mg *[see Warnings and Precautions (5.3), Drug Interactions (7.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)]*.

2.4 Patients with Hepatic Impairment

Because the safety and efficacy of the increased exposure to XENAZINE and other circulating metabolites are unknown, it is not possible to adjust the dosage of XENAZINE in hepatic impairment to ensure safe use. Therefore, XENAZINE is contraindicated in patients with hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.16), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

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 biplanar tablets with beveled edges, non-scored, embossed on one side with "CL" and "12.5."

The 25 mg XENAZINE tablets are yellowish-buff, cylindrical biplanar 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 (7.6)]*. 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 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 medical 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, hypertonia 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 8% 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 (7.4)]*.

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 (8.9)]*.

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 Use in Specific Populations (8.9)]*.

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 (8.9)]*.

Reserpine

Reserpine binds irreversibly to VMAT2, and the duration of its effect is several days. The physician should wait for chorea to reemerge 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 if XENAZINE is being considered for a patient with previously detected breast cancer. Although amenorrhea, galactorrhea, gynecomastia and impotence can be caused by elevated serum prolactin concentrations, the clinical significance of elevated serum prolactin concentrations for most patients is unknown. Chronic increase in serum prolactin levels (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 dopamine depletion 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)]*
- Dysphagia *[see Warnings and Precautions (5.8)]*
- Sedation and somnolence *[see Warnings and Precautions (5.9)]*

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 compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During its development, XENAZINE was administered to 773 unique subjects and patients. The conditions and duration of exposure to XENAZINE varied greatly, and included single and multiple dose clinical pharmacology studies in healthy volunteers (n=259) and open-label (n=529) and double-blind studies (n=84) in patients.

In a randomized, 12-week, placebo-controlled clinical trial of HD subjects, adverse reactions (ARs) were more common in the XENAZINE group than in the placebo group. Forty-nine of 54 (91%) patients who received XENAZINE experienced one or more ARs at any time during the study. The ARs most commonly reported (over 10%, and at least 5% greater than placebo) were sedation/somnolence (31% vs. 3% on placebo), fatigue (22% vs. 13% on placebo), insomnia (22% vs. 0% on placebo), depression (19% vs. 0% on placebo), akathisia (19% vs. 0% on placebo), and nausea (13% vs. 7% on placebo).

Adverse Reactions Occurring in ≥4% Patients

The number and percentage of the most commonly reported AEs that occurred at any time during the study in ≥4% of XENAZINE-treated patients, and with a greater frequency than in placebo-treated patients, are presented in Table 1 in decreasing order of frequency within body systems for the XENAZINE group.

Table 1. Treatment Emergent Adverse Reactions in Patients Treated with XENAZINE and with a Greater Frequency than Placebo in the 12-Week, Double-Blind, Placebo-Controlled Trial of XENAZINE

Body System	AE Term	XENAZINE n=54 n (%)	Placebo n=30 n (%)
PSYCHIATRIC DISORDERS	Sedation/somnolence	17 (31%)	1 (3%)
	Insomnia	12 (22%)	-
	Depression	10 (19%)	-
	Anxiety/anxiety aggravated	8 (15%)	1 (3%)
	Irritability	5 (9%)	1 (3%)
	Appetite decreased	2 (4%)	-
	Obsessive reaction	2 (4%)	-
CENTRAL & PERIPHERAL NERVOUS SYSTEM	Akathisia	10 (19%)	-
	Balance difficulty	5 (9%)	-
	Parkinsonism/bradykinesia	5 (9%)	-
	Dizziness	2 (4%)	-
	Dysarthria	2 (4%)	-
	Gait unsteady	2 (4%)	-
	Headache	2 (4%)	1 (3%)
GASTROINTESTINAL SYSTEM DISORDERS	Nausea	7 (13%)	2 (7%)
	Vomiting	3 (6%)	1 (3%)
BODY AS A WHOLE – GENERAL	Fatigue	12 (22%)	4 (13%)
	Fall	8 (15%)	4 (13%)
	Laceration (head)	3 (6%)	-
	Ecchymosis	3 (6%)	-
RESPIRATORY SYSTEM DISORDERS	Upper respiratory tract infection	6 (11%)	2 (7%)
	Shortness of breath	2 (4%)	-
	Bronchitis	2 (4%)	-
URINARY SYSTEM DISORDERS	Dysuria	2 (4%)	-

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

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 patients taking strong CYP2D6 inhibitors *[see Dosage and Administration (2.3), Warnings and Precautions (5.2), Use in Specific Populations (8.8), 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 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), 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 (7.6), 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, 5.9, 5.11, 5.12) and Drug Interactions (7.5)]*.

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.

Tetrabenazine had no clear effects on embryo-fetal development when administered to pregnant rats throughout the period of organogenesis at oral doses up to 30 mg/kg/day (or 3 times the maximum recommended human dose [MRHD] of 100 mg/day on a mg/m^2 basis). Tetrabenazine had no effects on embryo-fetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day (or 12 times the MRHD on a mg/m^2 basis). Because neither rat nor rabbit dosed with tetrabenazine produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately addressed the potential effects of tetrabenazine on embryo-fetal development in humans.

When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. The no-effect dose for stillbirths and postnatal mortality was 0.5 times the MRHD on a mg/m^2 basis. Because rats dosed with tetrabenazine do not produce 9-desmethyl-beta-DHTBZ, a major human metabolite, this study may not have adequately assessed the potential effects of tetrabenazine 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 accordingly 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 (PMs) 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).

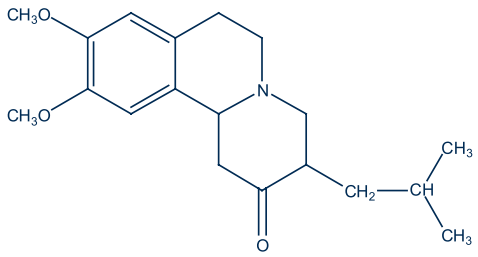
Abrupt discontinuation of XENAZINE from patients did not produce symptoms of withdrawal or a discontinuation syndrome; only symptoms of the original disease were observed to re-emerge *[see Dosage and Administration (2.5)]*.

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 1 g. 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 overdosage with any CNS-active drug. General supportive and symptomatic measures are recommended. Cardiac rhythm and vital signs should be monitored. In managing overdosage, the possibility of multiple drug involvement should always be considered. 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 (tetrabenazine) is a monoamine depletor for oral administration. The molecular weight of tetrabenazine is 317.43; the pKa is 6.51. Tetrabenazine is a hexahydro-dimethoxy-benzoquinolizine derivative and has the following chemical name: cis rac –1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-(2-methylpropyl)-2H-benzo[a]quinolizin-2-one.

The empirical formula $C_{19}H_{27}NO_3$ is represented by the following structural formula:



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

Each XENAZINE (tetrabenazine) Tablet contains either 12.5 or 25 mg of tetrabenazine as the active ingredient.

XENAZINE (tetrabenazine) Tablets contain tetrabenazine 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 (tetrabenazine) 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 (tetrabenazine) 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. Tetrabenazine reversibly inhibits the human vesicular monoamine transporter type 2 (VMAT2) ($K_i \approx 100$ nM), resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine stores. Human VMAT2 is also inhibited by dihydrotetrabenazine (HTBZ), a mixture of α-HTBZ and β-HTBZ. α- and β-HTBZ, major circulating metabolites in humans, exhibit high *in vitro* binding affinity to bovine VMAT2. Tetrabenazine 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 (7.5, 7.6), and Use in Specific Populations (8.9)]*.

Melanin Binding

Tetrabenazine or its metabolites bind to melanin-containing tissues (i.e., eye, skin, fur) in pigmented rats. After a single oral dose of radiolabeled tetrabenazine, 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 tetrabenazine, the extent of absorption is at least 75%. After single oral doses ranging from 12.5 to 50 mg, plasma concentrations of tetrabenazine are generally below the limit of detection because of the rapid and extensive hepatic metabolism of tetrabenazine 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 ^{11}C-labeled tetrabenazine or α-HTBZ, with the highest binding in the striatum and lowest binding in the cortex.

The *in vitro* protein binding of tetrabenazine, α-HTBZ, and β-HTBZ was examined in human plasma for concentrations ranging from 50 to 200 ng/mL. Tetrabenazine 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 tetrabenazine 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 tetrabenazine, 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 tetrabenazine nor its α- or β-HTBZ metabolites are likely to result in clinically significant induction of CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19.

Neither tetrabenazine 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, tetrabenazine 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 tetrabenazine 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 tetrabenazine 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 tetrabenazine. In patients with hepatic impairment, tetrabenazine plasma concentrations were similar to or higher than concentrations of α-HTBZ, reflecting the markedly decreased metabolism of tetrabenazine to α-HTBZ. The mean tetrabenazine 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 tetrabenazine 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 30-39% greater in patients with liver impairment than in age-matched controls. The safety and efficacy of this increased exposure to tetrabenazine and other circulating metabolites are unknown so that it is not possible to adjust the dosage of tetrabenazine in hepatic impairment to ensure safe use. Therefore, tetrabenazine is contraindicated in patients with hepatic impairment. *[see 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 tetrabenazine and its metabolites was studied in 25 healthy subjects following a single 50 mg dose of tetrabenazine 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 tetrabenazine compared to tetrabenazine given alone. For β-HTBZ, the C_{max} and AUC were increased 2.4- and 9-fold, respectively, in subjects given paroxetine prior to tetrabenazine given alone. The elimination half-life of α-HTBZ and β-HTBZ was approximately 14 hours when tetrabenazine 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), 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 (7.2)]*.

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), Warnings and Precautions (5.12), and Drug Interactions (7.3)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No increase in tumors was observed in $p53^{+/-}$ transgenic mice treated orally with tetrabenazine at doses of 0, 5, 15 and 30 mg/kg/day for 26 weeks. When compared to humans receiving a 50 mg dose of XENAZINE, mice dosed with a 30 mg/kg dose of tetrabenazine produce about one sixth the levels of 9-desmethyl-beta-DHTBZ, a major human metabolite. Therefore, this study may not have adequately characterized the potential of tetrabenazine to be carcinogenic in people.

Mutagenesis

Tetrabenazine and metabolites α-HTBZ and β-HTBZ were negative in the *in vitro* bacterial reverse mutation assay. Tetrabenazine was clastogenic in the *in vitro* chromosome aberration assay in Chinese hamster ovary cells in the presence of metabolic activation. α-HTBZ and β-HTBZ were clastogenic in the *in vitro* chromosome aberration assay in Chinese hamster lung cells in the presence and absence of metabolic activation. *In vivo* micronucleus tests were conducted in male and female rats and male mice. Tetrabenazine was negative in male mice and rats but produced an equivocal response in female rats.

Because the bioactivation system used in the *in vitro* studies was hepatic S9 fraction prepared from rat, a species that, when dosed with tetrabenazine, does not produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately assessed the potential of XENAZINE to be mutagenic in humans. Furthermore, since the mouse produces very low levels of this metabolite when dosed with tetrabenazine, the *in vivo* study may not have adequately assessed the potential of XENAZINE to be mutagenic in humans.

Impairment of Fertility

Oral administration of tetrabenazine (doses of 5, 15, or 30 mg/kg/day) to female rats prior to and throughout mating, and continuing through day 7 of gestation resulted in disrupted estrous cyclicity at doses greater than 5 mg/kg/day (less than the MRHD on a mg/m² basis).

No effects on mating and fertility indices or sperm parameters (motility, count, density) were observed when males were treated orally with tetrabenazine (doses of 5, 15 or 30 mg/kg/day; up to 3 times the MRHD on a mg/m² basis) prior to and throughout mating with untreated females.

Because rats dosed with tetrabenazine do not produce 9-desmethyl-beta-DHTBZ, a major human metabolite, these studies may not have adequately assessed the potential of XENAZINE to impair fertility in humans.

14 CLINICAL STUDIES

Study 1

The efficacy of XENAZINE as a treatment for the chorea of Huntington's disease was established primarily in a randomized, double-blind, placebo-controlled multi-center trial (Study 1) conducted in ambulatory patients with a diagnosis of HD. The diagnosis of HD was based on family history, neurological exam, and genetic testing. Treatment duration was 12 weeks, including a 7-week dose titration period and a 5-week maintenance period followed by a 1-week washout. The dose of XENAZINE was started at 12.5 mg per day and titrated upward at weekly intervals in 12.5 mg increments until satisfactory control of chorea was achieved, until intolerable side effects occurred, or until a maximal dose of 100 mg per day was reached.

The primary efficacy endpoint was the Total Chorea Score, an item of the Unified Huntington's Disease Rating Scale (UHDRS). On this scale, chorea is rated from 0 to 4 (with 0 representing no chorea) for 7 different parts of the body. The total score ranges from 0 to 28.

As shown in Figure 1, Total Chorea Scores for subjects in the drug group declined by an estimated 5.0 units during maintenance therapy (average of Week 9 and Week 12 scores versus baseline), compared to an estimated 1.5 units in the placebo group. The treatment effect of 3.5 units was statistically significant. At the Week 13 follow-up in Study 1 (1 week after discontinuation of the study medication), the Total Chorea Scores of subjects receiving XENAZINE returned to baseline.

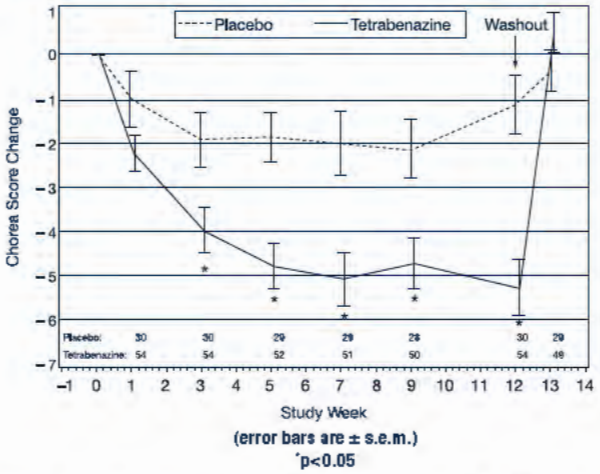


Figure 1. Mean ± s.e.m. Changes from Baseline in Total Chorea Score in 84 HD Subjects Treated with XENAZINE (n=54) or Placebo (n=30)

Figure 2 illustrates the cumulative percentages of patients from the XENAZINE and placebo treatment groups who achieved the level of reduction in the Total Chorea Score shown on the X axis. The left-ward shift of the curve (toward greater improvement) for XENAZINE-treated patients indicates that these patients were more likely to have any given degree of improvement in chorea score. Thus, for example, about 7% of placebo patients had a 6-point or greater improvement compared to 50% of XENAZINE-treated patients. The percentage of patients achieving reductions of at least 10, 6, and 3-points from baseline to Week 12 are shown in the inset table.

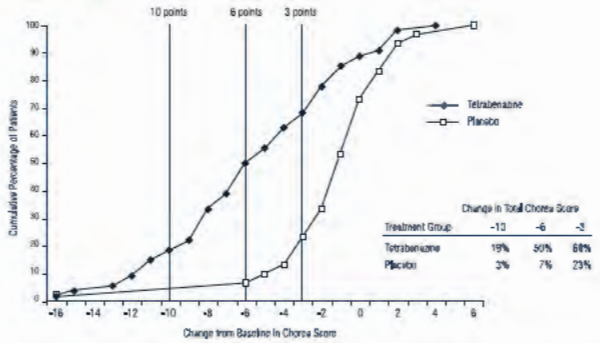


Figure 2. Cumulative Percentage of Patients with Specified Changes from Baseline in Total Chorea Score. The Percentages of Randomized Patients within each treatment group who completed Study 1 were: Placebo 97%, Tetrabenazine 91%.

A Physician-rated Clinical Global Impression (CGI) favored XENAZINE statistically. In general, measures of functional capacity and cognition showed no difference between XENAZINE and placebo. However, one functional measure (Part 4 of the UHDRS), a 25-item scale assessing the capacity for patients to perform certain activities of daily living, showed a decrement for patients treated with XENAZINE compared to placebo, a difference that was nominally statistically significant. A 3-item cognitive battery specifically developed to assess cognitive function in patients with HD (Part 2 of the UHDRS) also showed a decrement for patients treated with XENAZINE compared to placebo, but the difference was not statistically significant.

Study 2

A second controlled study was performed in patients who had been treated with open-label XENAZINE for at least 2 months (mean duration of treatment was 2 years). They were randomized to continuation of XENAZINE at the same dose (n=12) or to placebo (n=6) for three days, at which time their chorea scores were compared. Although the comparison did not reach statistical significance (p=0.1), the estimate of the treatment effect was similar to that seen in Study 1 (about 3.5 units).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XENAZINE (tetrabenazine) tablets are available in the following strengths and packages:

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

Bottles of 112: NDC 67386-421-01

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

Bottles of 112: NDC 67386-422-01

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide

Physicians are advised to discuss the following issues with patients and their families:

17.1 Risk of Suicidality

Patients and their families should be told that XENAZINE may increase the risk of suicidal thinking and behaviors. Patients and their families should be encouraged to be alert to the emergence of suicidal ideation and should report it immediately to the patient's physician *[see Contraindications (4), Warnings and Precautions (5.3), and Use in Specific Populations (8.7)]*.

17.2 Risk of Depression

Patients and their families should be told that XENAZINE may cause depression or may worsen pre-existing depression. They should be encouraged to be alert to the emergence of sadness, worsening of depression, withdrawal, insomnia, irritability, hostility (aggressiveness), akathisia (psychomotor restlessness), anxiety, agitation, or panic attacks and should report such symptoms promptly to the patient's physician *[see Contraindications (4), Warnings and Precautions (5.3), and Use in Specific Populations (8.7)]*.

17.3 Dosing of XENAZINE

Patients and their families should be told that the dose of XENAZINE will be titrated up slowly to the dose that is best for each patient. Sedation, akathisia, parkinsonism, depression, and difficulty swallowing may occur. Such symptoms should be promptly reported to the physician and the XENAZINE dose may need to be reduced or discontinued *[see Dosage and Administration (2.2), and Warnings and Precautions (5.3, 5.6, 5.7, 5.9)]*.

17.4 Risk of Sedation and Somnolence

Patients should be told that XENAZINE may induce sedation and somnolence and may 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 them to be alert, such as driving a car or operating machinery *[see Warnings and Precautions (5.9)]*.

17.5 Interaction with Alcohol

Patients and their families should be advised that alcohol may potentiate the sedation induced by XENAZINE *[see Warnings and Precautions (5.10)]*.

17.6 Usage in Pregnancy

Patients and their families should be advised to notify the physician if the patient becomes pregnant or intends to become pregnant during XENAZINE therapy, or is breast-feeding or intending to breast-feed an infant during therapy *[see Warnings and Precautions (5.14) and Use in Specific Populations (8.1)]*.

17.7 General Advice

Patients and their families should be advised to notify the physician of all medications the patient is taking and to consult with the physician before starting any new medications.

Manufactured by:
Recipharm Fontaine SAS
Rue des Près Potets
21121 Fontaine-les-Dijon
France

For:
Lundbeck
Deerfield, IL 60015, U.S.A.

Revised: September 2012

www.XenazineUSA.com

Xenazine®
(tetrabenazine)
12.5 and 25 mg Tablets

Note to Healthcare Professionals: Please provide this guide to your patient or your patient's caregiver.

What You Need to Know About Xenazine® (tetrabenazine)

Patient/Caregiver Counseling Guide

REACH™
Resources, Education, and Access for patients with Chorea associated with Huntington's disease

Xenazine®
(tetrabenazine)
12.5 and 25 mg Tablets

This guide explains Xenazine® (tetrabenazine) therapy, dosing, and potential side effects.

Table of Contents

What Is the Important Safety Information About Xenazine® (tetrabenazine)?

- Xenazine (*ZEN-uh-zeen*) is a prescription medicine to treat involuntary movements of Huntington's disease (HD). Involuntary movements, also called chorea, are a major feature of HD.
- Take Xenazine exactly as directed by your doctor. Take the prescribed dose of Xenazine at the correct time each day. Never take more Xenazine than your doctor has prescribed for you.
- The dose of Xenazine will be increased slowly to the dose that reduces chorea and is tolerated. Sleepiness, restlessness, parkinsonism (symptoms include slight shaking, body stiffness, trouble moving or keeping your balance), depression, and difficulty swallowing may occur.
- Xenazine does not cure the cause of chorea
- Xenazine does not treat other symptoms of HD, such as problems with thinking or emotions
- It is not known if Xenazine is safe and effective in children
- Xenazine is not for patients with HD who are depressed or who have depression that is not well controlled by medication
- Xenazine is not for patients who have thoughts of suicide
- Xenazine may increase your risk of developing depression or suicidal thoughts or of acting on these thoughts

Depression, thoughts of suicide, or suicide may occur in patients who have HD. The chance that these changes in mood or behavior may occur is increased in patients who are taking Xenazine.

What Are the Signs You May Be Depressed or at Risk for Suicide?

- Feel sad or have crying spells
- Lose interest in seeing your friends or doing things you used to enjoy
- Sleep a lot *more* or a lot *less* than usual
- Feel unimportant
- Feel guilty
- Feel hopeless or helpless
- Are more irritable, angry, or aggressive than usual
- Are *more* or *less* hungry than usual or notice a big change in your body weight
- Have trouble paying attention
- Feel tired or sleepy all the time
- Have thoughts about hurting yourself or ending your life

Talk to your doctor if you have any of the signs of depression listed above.

What Is Xenazine® (tetrabenazine)?

Xenazine is a medication taken by mouth to treat involuntary movements of HD. Involuntary movements, also called chorea, are a major feature of HD. These movements are typically quick, jerky, and irregular, and they can make it difficult to walk or sit still.

Xenazine may reduce chorea while you are taking it. In clinical studies, Xenazine reduced chorea in more than half the people who took it. Xenazine does not cure the cause of chorea, nor does it treat other symptoms of HD, such as problems with thinking or emotions.

How Does Xenazine Work?

Doctors are not sure what causes chorea or how Xenazine reduces chorea. Overactivity of a chemical in the brain, dopamine (*DOH-puh-meen*), may cause chorea. Xenazine can reduce the activity of dopamine in the brain, which may lessen chorea.

Who Should Not Take Xenazine?

Some people should not take Xenazine. Tell your doctor if any of these things are true for you.

Do not take Xenazine if you:

- Are sad (depressed) much of the time. See "What Is the Important Safety Information About Xenazine?" on page 2 for more details.
- Have liver problems
- Are taking monoamine oxidase (MAO) inhibitor medicine. **You must stop taking MAO inhibitors for at least 14 days before you begin treatment with Xenazine.**
  - Examples of MAO inhibitors are Nardil® (phenelzine), Eldepryl® (selegiline), and Parnate® (tranylcypromine)
- Are taking reserpine or medicine that contains reserpine. **You must stop taking reserpine for at least 20 days before you begin treatment with Xenazine.**
  - Examples of medicines that contain reserpine are Serpalan® or Renese®-R

If you are not sure if you are taking an MAO inhibitor or a medicine that contains reserpine, ask your doctor or pharmacist.

Before You Start to Take Xenazine® (tetrabenazine)

Tell Your Doctor About Your Health Problems

Tell your doctor about all your medical conditions, including any health problems you have now or had in the past. Taking Xenazine may make some health conditions worse.

Tell your doctor if you have any of these health conditions:

Physical conditions

- Liver problems
- Allergies to any of the ingredients in Xenazine tablets
  - Please see the Xenazine Medication Guide – General Information About Xenazine for a complete list of ingredients in Xenazine
- Breast cancer or a history of breast cancer
  - Xenazine may raise the level of the hormone prolactin. A high level of prolactin may affect some types of breast cancer.
- Irregular heartbeat (cardiac arrhythmia)
- Pregnant or plan to become pregnant
  - The effect of Xenazine on an unborn baby is not known
- Nursing a baby
  - It is not known if Xenazine passes into breast milk

Emotional or mental health conditions

- Sadness or depression
- Past thoughts of suicide or suicide attempts
- Nervousness or anxiety
- Anger or agitation
- Problems with your mental health

Tell Your Doctor and Pharmacist Which Medications You Are Taking

It is very important that you tell your doctor and pharmacist all the medications you are taking, including prescription medicines, nonprescription remedies, vitamins, and herbal products. Xenazine may interact with some medications, sometimes causing serious side effects. If you take certain drugs, your doctor may make a change in your dose of Xenazine.

Know the medicines you take. Keep a list of all of them and the dose for each to show your doctor. While you are taking Xenazine, talk to your doctor before you:

- Start taking any new medications
- Change the dose of any of your medications
- Stop taking any of your medications

What to Expect When Taking Xenazine® (tetrabenazine)

Getting Started on Xenazine

- When you start taking Xenazine, your doctor may increase your dose each week. You will follow this schedule for several weeks until you and your doctor find the dose you can tolerate that reduces your chorea.
- Take Xenazine exactly as directed by your doctor. Never take more or less Xenazine than your doctor has prescribed for you. Take the prescribed dose of Xenazine at the correct time each day.
- Xenazine is a tablet you take by mouth. You may take it with or without food. Xenazine is available in 2 strengths: a white tablet with 12.5 mg of Xenazine and a pale yellow tablet with 25 mg of Xenazine.
- Your doctor will start you on a low dose of Xenazine: 12.5 mg every morning for the first week
- The second week, your doctor may increase your daily dose of Xenazine to 25 mg:
  - 12.5 mg in the morning and another 12.5 mg 12 hours later in the evening
- If your daily dose is increased to 37.5 mg or 50 mg, you will need to take Xenazine 3 times a day
- For most patients, the maximum recommended daily dose is 100 mg. For some patients, the maximum daily dose may be 50 mg.
- **If your doctor thinks you need to take more than 50 mg of Xenazine each day, you will need a blood test to see if that dose is safe for you**

Skipping or Stopping Xenazine

- You should talk to your doctor about what to do if you miss a dose. If you have missed the previous dose and it is time for your next dose, do not double the dose.
- If you stop taking Xenazine, your chorea may return or worsen 12 to 18 hours after you took the last dose
- Tell your doctor if you stop taking Xenazine for more than 5 days. Do not take another dose until you talk to your doctor.

While Taking Xenazine

Because the most common side effect of Xenazine is sleepiness (sedation), take these precautions:

- Do not drive a car or operate dangerous machinery until you know how Xenazine affects you
- Drinking alcohol and taking other drugs that may also cause sleepiness while you are taking Xenazine may increase any sleepiness caused by Xenazine

Monitor Your Treatment With Xenazine® (tetrabenazine)

You should also tell your doctor if Xenazine is helping you. Be sure you understand what your doctor tells you. Ask questions until everything is clear. To help you remember, write down what your doctor tells you.

You and your caregiver should be alert for possible side effects with Xenazine.

Call your doctor if you have any of the side effects listed below or any other possible side effects not listed. Your doctor may lower the dose of Xenazine you are taking or prescribe a medicine to help with the side effect.

Do not stop taking Xenazine without talking to your doctor first.

What Are the Possible Side Effects With Xenazine?

Xenazine can cause serious side effects, including:

- **Depression or thoughts of suicide**. Xenazine may worsen your mood or ability to think clearly. It may be difficult to tell if these side effects are due to HD or Xenazine.

  Xenazine increases the chance of developing depression, having thoughts of suicide, or attempting suicide. You and your caregiver should be alert to these changes and tell your doctor if they occur. (See "What Is the Important Safety Information About Xenazine?" on page 2.)

Tell your doctor at once if you become depressed or have thoughts about suicide while taking Xenazine.

- **Neuroleptic malignant syndrome**. Neuroleptic malignant syndrome (NMS) is a very serious but rare side effect of Xenazine. Call your doctor at once and go to the nearest hospital emergency room if you develop these signs of NMS and they have no other obvious cause.

  The signs of NMS are:

  - High fever
  - Stiff muscles
  - Problems thinking
  - Very fast or uneven heartbeat
  - Increased sweating

- **Parkinsonism**. The signs of parkinsonism include slight shaking, body stiffness, and trouble moving or keeping your balance. Because body stiffness can develop as part of HD, it may be difficult to tell if this side effect is due to HD or Xenazine. If you develop the signs of parkinsonism, your doctor may reduce your dose of Xenazine or stop treatment with Xenazine.

- **Restlessness**. You may begin to feel a strong urge to move. This feeling may be a sign that you are developing a condition called akathisia. Tell your doctor if you have this feeling.

- **Trouble swallowing**. Xenazine® (tetrabenazine) may increase the chance that you will have trouble swallowing. Increased coughing may be the first sign that you are having trouble swallowing. Trouble swallowing increases your risk of pneumonia. Tell your doctor if you have trouble swallowing before you start or during your treatment with Xenazine.
- **Irregular heartbeat**. Xenazine increases your chance of having certain changes in the electrical activity in your heart that can be seen on an electrocardiogram (EKG). These changes can lead to a dangerous abnormal heartbeat. Taking Xenazine with certain medicines may increase this chance.
- **Dizziness**. Dizziness can occur when you change positions (sit up or stand up). This may happen because your blood pressure changes when you change positions. Xenazine may cause you to feel dizzy when you stand up.

  You should change positions slowly from lying down to sitting up and from sitting up to standing while you are taking Xenazine. Tell your doctor right away if you get dizzy or faint while taking Xenazine. Your doctor may monitor your blood pressure closely.
- **Tardive dyskinesia**. Tardive dyskinesia (TD) is a condition that may develop in patients treated with drugs that work like Xenazine.

  TD is a condition where there is repeated facial grimacing that cannot be controlled. These movements may include sticking out the tongue, smacking the lips, puckering and pursing the lips, and rapid eye blinking. Rapid movements of the arms, legs, and body may also occur.

  If you get TD while taking Xenazine, it is possible that the TD will not go away. The chance of developing TD and the chance that it will not go away appear to increase the longer you are being treated. There is no known treatment for TD, although it may partially or completely go away if you stop taking Xenazine.

The Most Common Side Effects That May Develop With Xenazine

The most common side effects with Xenazine include:

- Sleepiness (sedation)
- Trouble sleeping
- Depression
- Tiredness (fatigue)
- Anxiety
- Restlessness
- Agitation
- Nausea

Tell your doctor if you have any side effects. Do not stop taking Xenazine without talking to your doctor first.

Understanding Your Treatment With Xenazine® (tetrabenazine)

You will be given 2 guides to help you understand your therapy with Xenazine. This is the first guide, **What You Need to Know About Xenazine: Patient/Caregiver Counseling Guide**, which tells you about your treatment with Xenazine.

You will also be given the **Xenazine Medication Guide** every time your prescription is filled. The Medication Guide is a short version of this guide. Read the Medication Guide that comes with Xenazine before you start taking it and each time you refill the prescription. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

For more information on your treatment with Xenazine, call the Xenazine Information Center at 1-888-882-6013 or visit www.XenazineUSA.com.

You Are Not Alone

Call the people listed below any time you have a question or are worried about your treatment with Xenazine. Talking to them may help you. Keep their phone numbers near your telephone.

- Your doctor or nurse: _____
- The toll-free Xenazine Information Center: 1-888-882-6013

Notes:

Notes:

Xenazine®
(tetrabenazine)
12.5 and 25 mg Tablets

Reference ID: 3351234

Xenazine® (tetrabenazine) Tablets

Initial Dosing Plan

Prescriber should fill in as appropriate and provide to patient

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
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					

Call your doctor right away if you have any of the following symptoms:

- Feel sad or have crying spells
- Lose interest in seeing your friends or doing things you used to enjoy
- Sleep a lot *more* or a lot *less* than usual
- Feel unimportant
- Feel guilty
- Feel hopeless or helpless
- Are more irritable, angry, or aggressive than usual
- Are *more* or *less* hungry than usual or notice a big change in your body weight
- Have trouble paying attention
- Feel tired or sleepy all the time
- Have thoughts about hurting yourself or ending your life

If your doctor thinks you need to take more than 50 mg of Xenazine each day, you will need to have a blood test to see if that dose is safe for you.

How Should I Take Xenazine?

Xenazine is a pill you take by mouth. You may take it with or without food.

There are 2 strengths of Xenazine:

- A white pill with 12.5 mg of Xenazine
- A pale yellow pill with 25 mg of Xenazine

Tablets not actual size

Take Xenazine exactly as directed by your doctor. Never take more or less Xenazine than your doctor has prescribed for you. Take the prescribed dose of Xenazine at the correct time each day.

Xenazine®
(tetrabenazine)
12.5 and 25 mg Tablets

Getting Started on Xenazine

- When you start taking Xenazine, your doctor may increase your dose each week. You will follow this schedule for several weeks until you and your doctor find the dose you can tolerate that reduces your involuntary movements (chorea) of Huntington's disease.
- Your doctor will start you on a low dose of Xenazine: 12.5 mg every morning for the first week.
- The second week, your doctor may increase your daily dose of Xenazine to 25 mg: 12.5 mg in the morning and another 12.5 mg 12 hours later in the evening.
- If your daily dose is increased to 37.5 mg or 50 mg, you will need to take Xenazine 3 times a day.
- For most patients, the maximum recommended daily dose is 100 mg. For some patients, the maximum daily dose may be 50 mg.
- **If your doctor thinks you need to take more than 50 mg of Xenazine each day, you will need a blood test to see if that dose is safe for you.**

Skipping or Stopping Xenazine

- Before starting Xenazine, you should talk to your healthcare provider about what to do if you miss a dose. If you miss a dose and it is time for your next dose, do not double the dose.
- If you stop taking Xenazine, your chorea may return or worsen 12 to 18 hours after you took the last dose.
- Tell your doctor if you stop taking Xenazine for more than 5 days. Do not take another dose until you talk to your doctor.

Do You Have Questions About Your Treatment With Xenazine?

Call the Xenazine Information Center any time you have questions or worries: 1-888-882-6013

For more information about Xenazine, visit our website at www.XenazineUSA.com

Lundbeck

www.XenazineUSA.com

Xenazine® (tetrabenazine) 12.5 and 25 mg Tablets

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/s/

ALICE HUGHES
08/02/2013