CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-894

LABELING

Xenazine®
(tetrabenazine)
Tablets

Depression and Suicidality

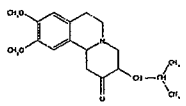
XENAZINE can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of XENAZINE must balance the risks of depression and suicidality with the clinical need for control of choreiform movements. Close observation 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; WARNINGS - Increased Risk of Depression and Suicidality, and PRECAUTIONS - Information for Patients).

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, maize starch, talc, and magnesium stearate. 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 tetrabenazine, or as a white non-scored tablet containing 12.5-mg of tetrabenazine.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The precise mechanism by which 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).

QTc Prolongation: The effect of a single 25 or 50 mg dose of tetrabenazine 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, tetrabenazine 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 tetrabenazine does not further increase the effect on the QTc interval. Effects at higher exposures to either tetrabenazine or its metabolites have not been evaluated. (See PRECAUTIONS - QTc Prolongation).

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.

Pharmacokinetics

Absorption and Distribution: 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 to 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 and β-HTBZ are subsequently metabolized to another major circulating metabolite, O-dealkylated-HTBZ, for which C_{max} is reached approximately 2 hours post-dosing.

The effects of food on the bioavailability of tetrabenazine 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.

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 and Excretion: α-HTBZ and β-HTBZ, major circulating metabolites, have half-lives of 4-8 hours and 2-4 hours, respectively. 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. β-HTBZ is O-dealkylated principally by CYP2D6.

After oral administration in humans, at least 19 metabolites of tetrabenazine have been identified. O-dealkylated HTBZ, α-HTBZ, and β-HTBZ are the major circulating metabolites, and they are subsequently metabolized to sulfate or glucuronide conjugates. CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP2E1 do not play a major role in metabolism of α-HTBZ or β-HTBZ based on *in vitro* studies.

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, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. Their effect on CYP2B6 has not been evaluated. *In vitro* studies suggest that neither tetrabenazine nor its α- or β-HTBZ metabolites is 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*.

Excretion: After oral administration, tetrabenazine is extensively hepatically metabolized, and the metabolites are primarily renally eliminated. 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.

Special Populations

Pediatrics: The pharmacokinetics of tetrabenazine and its primary metabolites have not been studied in pediatric subjects.

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

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

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

Renal Disease: The effect of renal insufficiency on the pharmacokinetics of tetrabenazine and its primary metabolites has not been studied.

Liver Disease: 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 CONTRAINDICATIONS; PRECAUTIONS - Use in Patients with Concomitant Illness; and DOSAGE AND ADMINISTRATION).

CYP2D6 Poor Metabolizers

Although the pharmacokinetics of tetrabenazine 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 compared to subjects who express the enzyme (extensive metabolizers, EMs), with an increase similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively). (see PRECAUTIONS - Drug Interactions and DOSAGE AND ADMINISTRATION). Patients should be genotyped for CYP2D6 prior to treatment with daily doses of tetrabenazine over 50 mg (see PRECAUTIONS - Laboratory Tests). Patients who are PMs should not be given daily doses greater than 50 mg. (see DOSAGE AND ADMINISTRATION)

Drug Interactions

α-HTBZ and β-HTBZ are metabolized principally by CYP2D6. A strong CYP2D6 inhibitor (paroxetine) markedly increases exposure to these metabolites (see PRECAUTIONS - Drug Interactions).

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

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 Huntington's disease (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/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 highly 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.

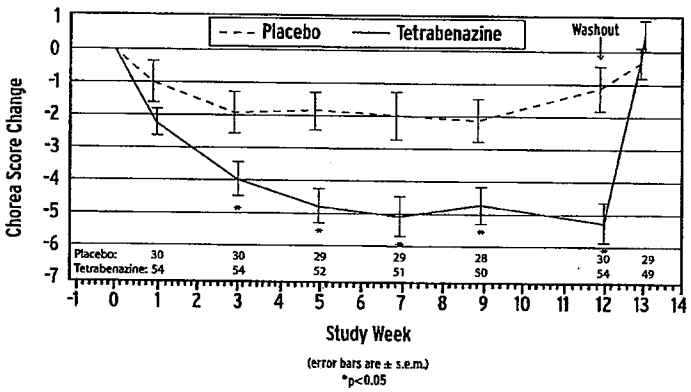


Figure 1. Mean ± s.e.m. Changes from Baseline in Total Chorea Score in 84 HD Subjects Treated with Tetrabenazine (n = 54) or Placebo (n = 30)

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 tetrabenazine-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 tetrabenazine-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.

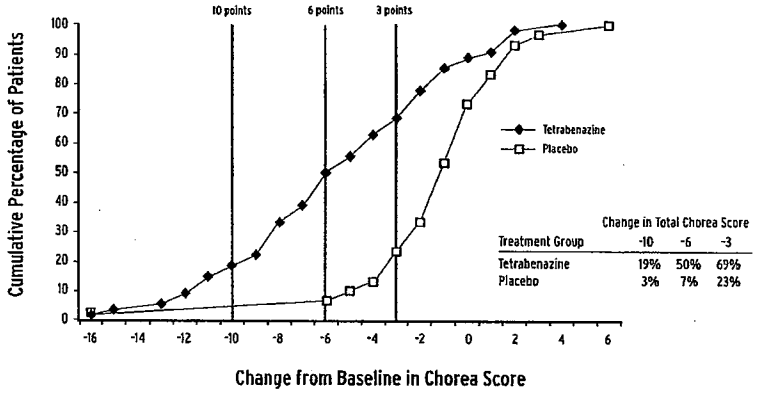


Figure 2. Cumulative Percentage of Patients with Specified Changes from Baseline in Total Chorea Score. The Percentages of Randomized Patients within each treatment group who completed Study I were: Placebo 97%, Tetrabenazine 91%.

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 tetrabenazine 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 tetrabenazine 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).

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

XENAZINE is contraindicated in patients who are actively suicidal, or in patients with untreated or inadequately treated depression. XENAZINE is contraindicated in patients with impaired hepatic function. XENAZINE is contraindicated in patients taking monoamine oxidase inhibitors. Xenazine is contraindicated in patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting XENAZINE (see PRECAUTIONS–Drug Interactions).

WARNINGS

Huntington's disease is a progressive disorder characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time. Although XENAZINE has been shown to decrease the chorea of HD in a 12-week controlled trial, it was also shown to cause slight worsening in mood, cognition, rigidity, and functional capacity. Whether these effects persist, resolve, or worsen with continued treatment is unknown. 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 choreiform movements 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.

Need for Careful Dosing of Xenazine

Proper dosing of XENAZINE involves careful 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 well tolerated (see DOSAGE AND ADMINISTRATION). 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, consideration should be given to discontinuing tetrabenazine.

Doses above 50 mg should not be given without CYP2D6 genotyping (see WARNINGS: Laboratory Tests and PRECAUTIONS – Drug Interactions).

Risk of Depression and Suicidality

Patients with Huntington's disease are at increased risk for depression and suicidal ideation and behavior (suicidality). Tetrabenazine increases these risks. All patients treated with tetrabenazine should be observed closely for new or worsening depression or suicidality.

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 tetrabenazine 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 tetrabenazine (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%; over 25% of patients attempt suicide at some point in the 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. (See PRECAUTIONS - Information for Patients).

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

Caution should be exercised in treating patients with XENAZINE who have a history of depression or prior suicide attempts or ideation, as these patients may be at increased risk for suicidal behavior (See PRECAUTIONS - Information for Patients). Patients who are actively suicidal or with untreated or inadequately treated depression should not be treated with tetrabenazine (see CONTRAINDICATIONS)

Antidepressants that are strong CYP2D6 inhibitors significantly increase exposure to α- and β-HTBZ. (see PRECAUTIONS–Drug Interactions)

Laboratory Tests

Before patients are given a daily dose of greater than 50 mg, they should be tested for the CYP2D6 gene to determine whether they are poor metabolizers (PMs) or extensive or intermediate metabolizers (EMs or IMs). When a dose of tetrabenazine is given to PMs, exposure will be substantially higher (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than it would be in EMs. The dosage should therefore be adjusted according to a patient's CYP2D6 metabolizer status by limiting the dose to 50 mg in patients who are CYP2D6 poor metabolizers. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with tetrabenazine 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 diagnostic evaluation of patients with this syndrome is complicated. In arriving at the diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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

If the patient requires treatment with tetrabenazine after recovery from NMS, the potential reintroduction of therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

PRECAUTIONS

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.

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 tetrabenazine, 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. The latter symptom 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. XENAZINE and other drugs that reduce dopaminergic transmission should be used with caution in patients with Huntington's disease at risk for aspiration pneumonia.

Sedation and Somnolence

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

Patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, until they are on a maintenance dose of tetrabenazine and know how the drug affects them (see PRECAUTIONS - Information for Patients).

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- Pharmacodynamics). The use of XENAZINE should be avoided in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, 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.

Concomitant Use of Neuroleptic Drugs

Patients taking neuroleptic drugs (e.g., haloperidol, chlorpromazine, risperidone, olanzapine) were excluded from clinical studies during the tetrabenazine development program. Adverse reactions associated with tetrabenazine, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists.

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 Information for Patients).

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 tetrabenazine-treated patients (vs. none on placebo) in the 12-week controlled trial; blood pressure was not measured during these events. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension.

Hyperprolactinemia

Tetrabenazine 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 tetrabenazine 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 tetrabenazine 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 tetrabenazine.

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 tetrabenazine, 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 tetrabenazine 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.

Use in Patients With Concomitant Illness

Clinical experience with tetrabenazine in patients with systemic illnesses is limited. Caution is advised in using tetrabenazine in patients with a history of depression or suicidality (see WARNINGS - Risk of Depression and Suicide). Caution is also advised in using tetrabenazine in patients with diseases, conditions, or treatments that could cause depression or increased suicidality. Tetrabenazine is contraindicated in patients with hepatic impairment (See CONTRAINDICATIONS and CLINICAL PHARMACOLOGY - Special Populations) and in patients with untreated or inadequately treated depression or who are actively suicidal.

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

Binding to Melanin-Containing Tissues

Since tetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that tetrabenazine may cause toxicity in these tissues after extended use. Neither ophthalmologic nor microscopic examination of 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 tetrabenazine'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.

Information for Patients

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

Patients and their families should be told that XENAZINE may increase the risk of patients considering or attempting suicide. 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.

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.

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 may require dose reduction or tetrabenazine discontinuation.

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.

Patients and their families should be advised that alcohol may potentiate the sedation induced by XENAZINE.

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.

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.

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. Caution should be used when giving any strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine) to a patient already receiving a stable dose of tetrabenazine, and the daily dose of tetrabenazine should be halved (see DOSAGE AND ADMINISTRATION). The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline has not been evaluated. (See DOSAGE AND ADMINISTRATION)

Other Cytochrome P450 inhibitors: Based on *in vitro* studies, a clinically significant interaction between tetrabenazine and other P450 inhibitors (other than CYP2D6 inhibitors) is not likely. (See CLINICAL PHARMACOLOGY)

Reserpine: Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Caution should therefore be used when switching a patient from reserpine to XENAZINE. The physician should wait for chorea to re-emerge 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).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Lifetime carcinogenicity studies have not been conducted with tetrabenazine.

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.

Impairment of Fertility: Fertility and early embryonic development studies have not been conducted with tetrabenazine.

Pregnancy: Pregnancy Category C

Tetrabenazine had no clear effects on embryo-fetal development when administered to pregnant rats throughout the period of organogenesis at oral doses up to 30 mg/kg/day (or 3 times the maximum recommended human dose [MRHD] of 100 mg/day on a mg/m² basis). 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/m² basis).

When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. The no-effect dose for stillbirths and postnatal mortality was 0.5 times the MRHD on a mg/m² basis.

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. (See Information for Patients)

Labor and Delivery

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

Nursing Mothers

It is not known whether tetrabenazine 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 tetrabenazine, a decision should be made whether to discontinue nursing or to discontinue tetrabenazine, taking into account the importance of the drug to the mother.

Pediatric Use

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

ADVERSE REACTIONS

During its development, tetrabenazine was administered to 773 unique subjects and patients. The conditions and duration of exposure to tetrabenazine 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.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of adverse effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

In a randomized, 12-week, placebo-controlled clinical trial of HD subjects, adverse events (AEs) were more common in the tetrabenazine group than in the placebo group. Forty-nine of 54 (91%) patients who received XENAZINE experienced one or more AEs at any time during the study. The AEs 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). The number and percentage of the most commonly reported AEs that occurred at any time during the study in ≥4% of tetrabenazine-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 tetrabenazine group.

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

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

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

Table 2. Treatment Emergent Extrapyramidal Symptoms in Patients Treated with Tetrabenazine and 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.

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 ALT and AST laboratory values as compared to placebo.

Vital Signs

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Tetrabenazine is not a controlled substance.

Physical and Psychological Dependence

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 tetrabenazine has been marketed. Abrupt discontinuation of tetrabenazine from patients did not produce symptoms of withdrawal or a discontinuation syndrome; only symptoms of the original disease were observed to re emerge. 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 tetrabenazine misuse or abuse (such as development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

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

Overdose Management

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®).

DOSAGE AND ADMINISTRATION

In patients with chorea associated with Huntington's disease, proper dosing of XENAZINE involves careful 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 for chronic use that reduces chorea and is well tolerated. Doses above 100 mg/day are not recommended for any patient.

Dosing Recommendations up to 50 mg per day

The dose of XENAZINE should be individualized. 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, to allow the identification of a dose that reduces chorea and is well tolerated. 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 intolerable sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antidepressants).

Dosing Recommendations above 50 mg per day

Patients who appear to require doses greater than 50 mg per day should be genotyped for CYP2D6.

The dose of XENAZINE should be individualized.

For CYP2D6 Extensive and Intermediate Metabolizers (patients who express CYP2D6)

At doses above 50 mg per day, XENAZINE should be titrated up slowly at weekly intervals by 12.5 mg, to allow the identification of a dose that reduces chorea and is well tolerated. 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 intolerable sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antidepressants).

For CYP2D6 Poor Metabolizers (patients who do not express CYP2D6)

In patients who are CYP2D6 poor metabolizers, dosing is similar to EMs except that the recommended maximum single dose is 25 mg, and the maximum recommended daily dose is 50 mg.

Discontinuation of Treatment with XENAZINE

Treatment with XENAZINE can be discontinued without tapering. Re-emergence of chorea may occur within 12 to 18 hours after the last dose of tetrabenazine.

Resumption of Treatment

Following treatment interruption of greater than five (5) days or a treatment interruption occurring due to a change in the patient's medical condition or concomitant medications, XENAZINE therapy should be retitrated when resumed. For short-term treatment interruption of less than five (5) days, treatment can be resumed at the previous maintenance dose without titration.

SPECIAL POPULATIONS

Hepatically Impaired Patients: The use of XENAZINE in patients with liver disease is contraindicated (see CLINICAL PHARMACOLOGY - Hepatic Impairment and Special Populations under and CONTRAINDICATIONS and PRECAUTIONS - Use in Patients with Concomitant Illness).

Patients taking CYP2D6 Inhibitors

Caution should be used when adding a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine), to a patient already receiving a stable dose of tetrabenazine. In patients receiving co-administered strong CYP2D6 inhibitors, the daily dose of tetrabenazine should be halved. To initiate treatment with XENAZINE in patients on a stable dose of a strong CYP2D6 inhibitor, the dosing recommendations for the CYP2D6 poor metabolizers 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).

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 18722-001-01

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 18722-002-01

STORAGE

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

Distributed by:

Prestwick PHARMACEUTICALS

Prestwick Pharmaceuticals, Inc.
1825 K Street NW, Suite 1475
Washington, DC 20006

Issued May 2008

MEDICATION GUIDE

XENAZINE (*ZEN-uh-zeen*)
(tetrabenazine)
Tablets

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.

What is the most important information I should know about Xenazine?

- **Xenazine may increase the chance of depression, suicidal thoughts, or suicidal actions in some patients.**
- You should not start taking Xenazine if you are depressed (have untreated depression or depression that is not well controlled by medicine) **or** have suicidal thoughts.
- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts or feelings. This is especially important when Xenazine is started and when the dose is changed.

Call the doctor right away if you become depressed or have any of the following symptoms, especially if they are new, worse, or worry you:

- You feel sad or have crying spells.
- You are no longer interested in seeing your friends or doing things you used to enjoy.
- You are sleeping a lot *more* or a lot *less* than usual.
- You feel unimportant.
- You feel guilty.
- You feel hopeless or helpless.
- You are more irritable, angry, or aggressive than usual.
- You are more or less hungry than usual or notice a big change in your body weight.
- You have trouble paying attention.
- You feel tired or sleepy all the time.
- You have thoughts about hurting yourself or ending your life.

What is Xenazine?

Xenazine is a medicine that is used to treat the involuntary movements (chorea) of Huntington's disease. Xenazine does not cure the cause of the involuntary movements, and it does not treat other symptoms of Huntington's disease, such as problems with thinking or emotions.

It is not known whether Xenazine is safe and effective in children.

Who should not take Xenazine?

Do not take Xenazine if you:

- are depressed or have thoughts of suicide. See "What is the most important information I should know about Xenazine?"
- have liver problems.

- are taking a monoamine oxidase inhibitor (MAOI) medicine. Ask your doctor or pharmacist if you are not sure.
- are taking reserpine. **Do not take medicines that contain reserpine (such as Serpalan® and Renese®-R) with Xenazine. If your doctor plans to switch you from taking reserpine to Xenazine, you must wait at least 20 days after your last dose of reserpine before you start taking Xenazine.**

What should I tell my doctor before taking Xenazine?

Tell your doctor about all your medical conditions, including if you:

- have emotional or mental problems (for example, depression, nervousness, anxiety, anger, agitation, psychosis, previous suicidal thoughts or suicide attempts).
- have liver disease.
- have any allergies. See the end of this Medication Guide for a complete list of the ingredients in Xenazine.
- have breast cancer or a history of breast cancer.
- have heart disease that is not stable, have heart failure or recently had a heart attack.
- have an irregular heart beat (cardiac arrhythmia).
- are pregnant or plan to become pregnant. It is not known if Xenazine can harm your unborn baby.
- are breast-feeding. It is not known if Xenazine passes into breast milk.

Tell your doctor about all the medicines you take, including prescription medicines and nonprescription medicines, vitamins and herbal products. Using Xenazine with certain other medicines may cause serious side effects. **Do not start <u>any</u> new medicines while taking Xenazine without talking to your doctor first.**

How should I take Xenazine?

- Xenazine is a tablet that you take by mouth.
- **Take Xenazine exactly as prescribed by your doctor.**
- You may take Xenazine with or without food.
- Your doctor will increase your dose of Xenazine each week for several weeks, until you and your doctor find the best dose for you.
- If you stop taking Xenazine or miss a dose, your involuntary movements may return or worsen in 12 to 18 hours after the last dose.
- Before starting Xenazine, you should talk to your health care 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.
- Tell your doctor if you stop taking Xenazine for more than 5 days. **Do not take another dose until you talk to your doctor.**
- **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 it is safe for you.**

What should I avoid while taking Xenazine?

Sleepiness (sedation) is a common side effect of Xenazine. While taking Xenazine **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.

What are the possible side effects of Xenazine?

Xenazine can cause serious side effects, including:

- **Depression, suicidal thoughts, or actions.** See "What is the most important information I should know about Xenazine?"
- **Neuroleptic Malignant Syndrome (NMS).** Call your doctor right away and go to the nearest emergency room if you develop these signs and symptoms that do not have another obvious cause:
  - high fever
  - stiff muscles
  - problems thinking
  - very fast or uneven heartbeat
  - increased sweating
- **Parkinsonism.** Symptoms of Parkinsonism include: slight shaking, body stiffness, trouble moving or keeping your balance.
- **Restlessness.** You may get a condition where you feel a strong urge to move. This is called akathisia.
- **Trouble swallowing.** Xenazine 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.
- **Irregular heartbeat.** Xenazine increases your chance of having certain changes in the electrical activity in your heart which 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 due to blood pressure changes when you change position (orthostatic hypotension).** Change positions slowly from lying down to sitting up and from sitting up to standing when taking Xenazine. Tell your doctor right away if you get dizzy or faint while taking Xenazine. Your doctor may need to watch your blood pressure closely.
- **Tardive dyskinesia (TD).** TD is a condition where there is repeated facial grimacing that cannot be controlled, sticking out of the tongue, smacking of the lips, puckering and pursing of the lips, and rapid eye blinking. Xenazine works like other drugs that can cause TD. If you get TD with Xenazine, it is possible that the TD will not go away.

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.

Call your doctor for medical advice about side effects. You may report side effects to the Food and Drug Administration (FDA) at 1-800-FDA-1088.

NDC 18722-001-01

Xenazine®
(tetrabenazine) Tablets
12.5 mg

Medication Guide Required: Each time Xenazine® is dispensed, give the patient a Medication Guide.

112 Tablets

Xenazine® is a registered trademark of Cambridge Laboratories (Ireland) Limited.

Rx Only

Usual Dosage:
Consult package insert for prescribing information.

Storage Conditions:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Distributed by:
Prestwick PHARMACEUTICALS
Washington, DC 20006

Rev. 0 (May 2008)

3 18722-001-01 5

Exp: FPO
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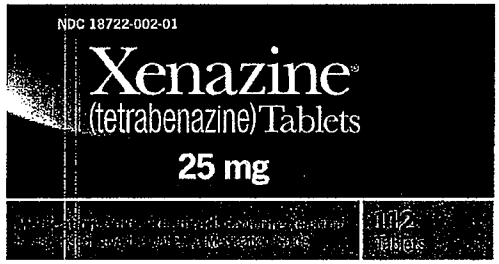

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Attachment A

NDA 21-894 Xenazine® (tetrabenazine)

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

To reduce the risk of drug-associated depression and suicidality in patients receiving Xenazine® (tetrabenazine), to promote informed prescribing and proper titration and dosing of tetrabenazine, and to minimize the risk of drug-drug interactions with strong CYP2D6 inhibitors.

II. REMS ELEMENTS

A. Medication Guide

In compliance with 21 CFR 208.24, Prestwick will institute the following measures:

- A Medication Guide will be dispensed with each tetrabenazine prescription.
- Three (3) Medication Guides will be attached to each Xenazine package.
- The package will also include a prominent notice to include a Medication Guide with each prescription in the event that less than a full bottle of Xenazine is prescribed.
- The "Dear Pharmacist" letter will include instructions to provide the Medication Guide with each prescription.
- Ten (10) Medication Guides will be included with the "Dear Pharmacist" letter.
- Medication Guides will be available via sales and/or clinical representatives, the product website or through the Sponsor toll-free medical information line.

B. Communication Plan

Prestwick 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. Prestwick will provide physicians and pharmacists with the educational 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®: A Healthcare Professional Guide
        v. Patient/Caregiver Counseling Guide
        vi. Initial Dosing Plan

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

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

3. Pharmacy Management Systems - Prestwick 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, Prestwick 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 material (to be cleared through DDMAC) will include information on the tetrabenazine REMS and will be used to reinforce the risk minimization messages 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®: 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 all pharmacists (based on a membership list from the American Pharmacists Association and the American Society of Health System Pharmacists) 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®: 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 annually and sent to all neurologists, movement disorder specialists and

pharmacists. These annual mailings will include the most current PI, *Prescribing Xenazine®: A Healthcare Professional Guide*, *What You Need to Know About Xenazine®: Patient/Caregiver Counseling Guide,* and Medication Guide.

C. Elements To Assure Safe Use

Tetrabenazine has been shown to be effective but is associated with risk of depression and suicidality. Tetrabenazine can be approved without any elements to assure safe use.

D. Implementation System

Because tetrabenazine can be approved without any elements to assure safe use, an implementation system is not required.

E. Timetable for Submission of Assessments

REMS Assessments (see B below for content) will be submitted to FDA no less frequently than at 12 months, 2 years, 3 years, and 7 years after approval.

III. Information Needed for Assessments

a. Results of the following two surveys to be conducted by Prestwick which will be designed to monitor the effectiveness of the interventions in educating prescribers on the proper use of tetrabenazine therapy, compliance with the titration and dosing guidelines contained in the labeling, and occurrence of targeted adverse events and their management by the prescriber:

   i. Prescriber Surveys

   Prestwick will conduct a survey in a representative sample of prescribers over two waves (as outlined below) to determine whether the educational interventions are effective in educating prescribers about how to titrate and dose tetrabenazine and how to monitor for and manage targeted adverse events. Each wave will include 25-30 healthcare professionals. The prescriber survey will be conducted six months after launch, and will be repeated 18 months after launch and periodically as needed, to be determined by FDA at the 2 year assessment. The survey instrument and methodology will be developed after the product labeling and the educational materials are finalized and will be provided to the FDA for review and comment at least 2 months before it is administered to prescribers in the field. The survey protocol will include the sample size and confidence intervals associated with that sample size; how the sample will be determined (selection criteria); the expected number of physicians to be surveyed; how the participants will be recruited; how and when the surveys will be administered; and an explanation of controls used to minimize bias.

ii. Patient and Caregiver Knowledge Survey

Prestwick will conduct a survey in a representative sample of patients and caregivers to determine whether the educational interventions are effective in educating patients and caregivers on: the importance of titration and the monitoring for targeted adverse events.

The patient and caregiver survey will be conducted in two waves, at approximately six months after launch, and 18 months after launch. There will be approximately 100 completed interviews at each wave. The survey will be repeated periodically as needed, to be determined by FDA at the 2 year assessment. The survey and methodology will be developed after the product labeling and the educational materials are finalized and will be provided to the FDA for review and comment at least 2 months before it is administered to patients and caregivers. The survey protocol will include the sample size and confidence intervals associated with that sample size; how the sample will be determined (selection criteria); the expected number of patients and caregivers to be surveyed; how the participants will be recruited; how and when the surveys will be administered; and an explanation of controls used to minimize bias.

b. Based on the results of the surveys and any other relevant information, Prestwick will provide an assessment and conclusion whether the REMS is meeting its goals and whether modifications to the REMS are needed.

Prestwick
PHARMACEUTICALS

[date]

[Name, MD
Institution name
Street address
City, state zip code]

Dear Healthcare Provider:

Xenazine® (tetrabenazine) is the first agent to be approved by the Food and Drug Administration (FDA) for the treatment of chorea associated with Huntington's disease (HD). Xenazine will be available for your patients next month.

Decisions to use Xenazine to treat chorea associated with HD must balance the potential benefits with the risks of therapy. Xenazine carries the following boxed 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; WARNINGS - Increased Risk of Depression and Suicidality, and PRECAUTIONS - Information for Patients).

You are advised to discuss the risks associated with Xenazine therapy with patients and their caregivers. We have enclosed a copy of the Xenazine *Medication Guide*, which will be provided to patients with every filled prescription. This *Medication Guide* contains information that can be used to facilitate discussions about risks of therapy. It also explains the titration schedule for initiating therapy with Xenazine.

Xenazine is contraindicated in patients who are actively suicidal or those who have untreated or inadequately treated depression. Xenazine is also contraindicated in patients with hepatic impairment and in patients taking a monoamine oxidase inhibitor or reserpine. At least 20 days should elapse after stopping reserpine before starting Xenazine.

Patients should be made aware of rare but serious adverse reactions that can potentially occur with Xenazine, such as neuroleptic malignant syndrome, tardive dyskinesia and QT prolongation–related arrhythmias.

The basis for FDA approval was a multicenter, placebo-controlled, 12-week study of Xenazine conducted in 84 patients with chorea associated with HD.[1] The most commonly observed drug-related adverse reactions in Xenazine-treated patients were sedation/somnolence (31%), fatigue (22%), insomnia (22%), depression (19%), akathisia (19%), and nausea (13%). Some adverse events may be dose dependent and may resolve or lessen with dose adjustment or specific treatment.

During this 12-week study, a significant reduction in chorea and a significant improvement on the physician-rated clinical global impression scale was observed during treatment with Xenazine. However, 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. As HD is characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time, it may be difficult to distinguish between drug-induced adverse events and progression of the underlying disease process. During long-term treatment, you should periodically reevaluate the need for Xenazine in your patients, assessing improvements in choreiform movements and monitoring for treatment-emergent adverse events. Periodic reevaluations should include special attention to developing depression, cognitive decline, parkinsonism, dysphagia, sedation, akathisia, restlessness, and functional disability.

Xenazine treatment should be initiated with careful titration to the dose appropriate for each patient (see DOSAGE AND ADMINISTRATION in the package insert). Close monitoring of dose titration should be conducted over several weeks to identify the dose that reduces chorea and is well tolerated for long-term therapy.

Please see the enclosed

- Xenazine package insert,
- *A Healthcare Professional Guide,*
- *A Patient/Caregiver Counseling Guide**,
- The *Medication Guide** and
- *An Initial Dosing Plan.** This card instructs the patient on how to titrate Xenazine during the first three weeks of treatment. For doses beyond 37.5 mg daily, you need to fill in the card.

*You need to give a copy of these documents to your patient or your patient's caregiver. For more information on how to use Xenazine to treat chorea associated with HD, or to schedule an appointment with a Prestwick National Account Manager, please call the Xenazine toll-free medical information line at 1-800-XXX-XXXX or visit us online at www.xxxxxxxx.com.

Sincerely,

David A. Stamler, MD
Chief Scientific Officer
Prestwick Pharmaceuticals, Inc.

Enclosures

Reference: 1. Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: A randomized controlled trial. *Neurology.* 2006;66(3):366-372.

Prestwick
PHARMACEUTICALS

[date]

[Name
Pharmacy name
Street address
City, State Zip code]

Dear Pharmacist:

Prestwick Pharmaceuticals, Inc. wishes to inform you of the introduction of Xenazine® (tetrabenazine) Tablets for the treatment of chorea associated with Huntington's disease (HD). **This letter serves to notify you that the Food and Drug Administration (FDA) requires that a *Medication Guide* be distributed directly to each patient to whom Xenazine is dispensed. Accordingly, as per FDA regulations, a copy of the enclosed Xenazine *Medication Guide* must be distributed to each patient who fills a prescription for Xenazine.** Enclosed are 10 copies of the Xenazine *Medication Guide* for distribution to patients.

Should you require additional copies of the Xenazine *Medication Guide*, you may

- Request copies from Prestwick by calling the Xenazine toll-free medical information line at 1-800-XXX-XXXX
- Print copies of the *Medication Guide* from the Xenazine web site as described below
- Request copies from your drug supplier
- Photocopy the enclosed *Medication Guide*, after confirming that it is the most current version by one of the following methods:
  - Going to the Xenazine web site at www.xxxxxxxxxx.com
  - Calling the Xenazine toll-free medical information line at the number above

Please see the important boxed warning about Xenazine at the end of this letter. Should you have questions concerning Xenazine product information, please call Prestwick at 1-800-XXX-XXXX. In addition, you can send adverse event information directly to Prestwick Safety Surveillance and Epidemiology (SSE) by fax to XXX-XXX-XXXX or by mail to SSE, [street address, City, State Zip code].

Adverse event information may also be reported to the FDA MedWatch Reporting System by the following methods:

- Online at www.fda.gov/medwatch/report.htm
- Phone at 1-800-FDA-1088
- Fax at 1-800-FDA-0178, using the MedWatch Form 3500 (available at www.fda.gov/medwatch/getforms.htm)
- Mail, using the postage-paid MedWatch Form 3500 (see above), to
  - MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787

Xenazine is contraindicated in patients who are actively suicidal or who have untreated or inadequately treated depression. Use of Xenazine is also contraindicated in patients with hepatic impairment and in patients taking a monoamine oxidase inhibitor or reserpine. At least 20 days should elapse after stopping reserpine before starting therapy with Xenazine.

Caution should be used when adding a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine) to a patient already receiving a stable dose of Xenazine. In such patients, the daily dose of Xenazine should be halved. To initiate treatment with Xenazine in patients on a stable dose of a strong CYP2D6 inhibitor, the maximum recommended daily dose of Xenazine is 50 mg. 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 the enclosed package insert).

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.

Proper dosing of Xenazine involves careful 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 for chronic use that reduces chorea and is well tolerated (see DOSAGE AND ADMINISTRATION in the enclosed package insert).

Production and distribution of Xenazine is currently underway, and it will be available for your patients next month. Xenazine will be available in bottles of 112 tablets, with an attached *Medication Guide*. Any exception to dispensing Xenazine in this package will require distribution of a Xenazine *Medication Guide*.

To help you understand Xenazine prescribing and to answer questions posed by patients, we are enclosing the following items:

- 10 copies of the *Medication Guide*
- The Xenazine package insert
- A guide for prescribers, *A Healthcare Professional Guide*, that outlines the Xenazine Risk MAP

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; WARNINGS - Increased Risk of Depression and Suicidality, and PRECAUTIONS - Information for Patients).

Sincerely,

David A. Stamler, MD
Chief Scientific Officer
Prestwick Pharmaceuticals, Inc.

Enclosures

Prescribing Xenazine® (tetrabenazine) Tablets

A Healthcare Professional Guide

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; WARNINGS - Increased Risk of Depression and Suicidality, and PRECAUTIONS - Information for Patients).

Table of Contents

The Most Important Information About Xenazine

Indication for Treatment With Xenazine

Xenazine® (tetrabenazine) Tablets are indicated for the treatment of chorea associated with Huntington's disease (HD).

Contraindications to Treatment With Xenazine

Xenazine is contraindicated in patients who are actively suicidal or who have untreated or inadequately treated depression. Xenazine is contraindicated in patients with hepatic impairment. Xenazine is contraindicated in patients taking a monoamine oxidase inhibitor or reserpine. At least 20 days should elapse after stopping reserpine before starting Xenazine.

Considerations When Treating HD Chorea With Xenazine

HD is an autosomal dominant neurodegenerative disorder characterized by chorea and changes in mood, cognition, rigidity, and functional capacity over time. Although Xenazine was shown to decrease the chorea of HD in a 12-week controlled trial, it was also shown to cause slight worsening in mood, cognition, rigidity, and functional capacity. Whether these effects persist, resolve, or worsen with continued treatment is unknown. Therefore, proper use of Xenazine requires attention to all facets of the underlying disease process during titration and long-term treatment.

During long-term treatment, you should periodically reevaluate the need for Xenazine in your patients, assessing improvements in choreiform movements and monitoring for treatment-emergent adverse events. Therefore, such periodic reevaluations should include special attention to developing depression, cognitive decline, parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and functional disability.

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 (see **Discontinuation of Treatment** and **Resumption of Treatment** on pages 7-8). In some patients, chorea may improve over time, decreasing the need for Xenazine.

Initiating Treatment With Xenazine

Xenazine treatment should be initiated with careful titration to the dose appropriate for each patient (see **Dosing Xenazine** on page 5). The starting dose of Xenazine is 12.5 mg per day. The daily dose should be increased by 12.5-mg increments each week until satisfactory control of chorea is achieved or adverse events occur. Close monitoring of dose titration should be conducted over several weeks to identify the dose that reduces chorea and is well tolerated for long-term therapy.

Some adverse events, such as depression, fatigue, insomnia, sedation/somnolence, parkinsonism, and akathisia, may be dose dependent and may resolve or lessen with dose adjustment or specific treatment. If resolution of the adverse event does not occur, consideration should be given to discontinuing Xenazine (see **Discontinuation of Treatment** on page 7).

Daily Doses Greater Than 50 mg

The CYP2D6 enzyme plays a major role in the metabolism of Xenazine. If daily doses of greater than 50 mg are necessary, patients should first be tested for the CYP2D6 gene to determine whether they are poor metabolizers (PMs) or extensive or intermediate metabolizers (EMs or IMs) of CYP2D6. When a dose of Xenazine is given to PMs, exposure will be substantially higher than it would be in EMs. The dosage should therefore be adjusted according to a patient's CYP2D6 metabolizer status. In patients who are PMs of CYP2D6, the maximum recommended daily dose is 50 mg. In patients who are EMs or IMs of CYP2D6, the maximum recommended daily dose is 100 mg.

Please refer to the Xenazine Prescribing Information on pages 9-16.

The Risk of Suicidality and New or Worsening Depression

Patients with HD are at increased risk for depression and suicidal ideation and behavior (suicidality). Xenazine increases 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 Huntington's disease, 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

If depression or suicidality occurs, the dose of Xenazine should be reduced. Initiating treatment with or increasing the dose of a concomitant antidepressant may also be useful. In patients with new-onset depression who require antidepressants that are strong CYP2D6 inhibitors (such as paroxetine and fluoxetine), the total dose of Xenazine should be halved (see **PRECAUTIONS** in the Prescribing Information on pages 9-16). If depression or suicidality does not resolve, consideration should be given to discontinuing treatment with Xenazine (see **Treatment Interruption or Discontinuation of Therapy** on pages 7-8).

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 therapy 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.

About Xenazine® (tetrabenazine) Tablets

Xenazine is a monoamine depletor that works by selectively blocking human vesicular monoamine transporter type 2 (VMAT2).

HD is an autosomal dominant neurodegenerative disorder affecting approximately 30,000 patients in the United States.[4] Chorea, a motor disorder characterized by involuntary movement, is a major feature of adult-onset HD.

Chorea can affect a patient's ability to carry out activities of daily living and can be a contributor to falls with associated injuries. It may increase the need for institutionalization. Chorea is often a socially disabling condition, leading patients, and potentially their families, to withdraw from social or community activities out of embarrassment or fear of being disruptive.

Xenazine should not be prescribed to

- Patients who are actively suicidal
- Patients with untreated or inadequately treated depression
- Patients with impaired hepatic function
- Patients taking monoamine oxidase inhibitors
- Patients taking reserpine

  At least 20 days should elapse after stopping therapy with reserpine before initiating therapy with Xenazine.

Please refer to the Xenazine Prescribing Information on pages 9-16.

The most common adverse events associated with Xenazine use include sedation/somnolence, fatigue, insomnia, depression, anxiety, akathisia or restlessness, and nausea.

Xenazine therapy should not be undertaken before the patient has been counseled about the warnings and precautions in the package insert. A patient information sheet, referred to as a *Medication Guide*, should be dispensed by the pharmacy to the patient with each prescription. However, the prescriber should provide a copy of this *Medication Guide* to the patient prior to the initiation of treatment. The prescriber should also provide *What You Need to Know About Xenazine (tetrabenazine): Patient/Caregiver Counseling Guide.* The prescriber should fill in the *Initial Dosing Plan* card as appropriate and provide it to the patient.

What Patients Should Know About Xenazine

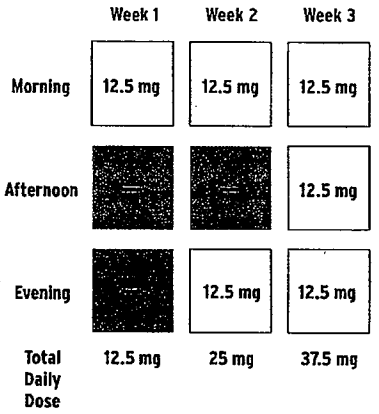
The following information should be discussed with patients and caregivers before initiating Xenazine (tetrabenazine) Tablets therapy:

- Patients and their families should be told 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. Such symptoms should be reported immediately to the patient's physician.
- Patients and their families should be told that Xenazine may cause depression or may worsen pre-existing 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. Such symptoms should be reported immediately to the patient's physician.
- Patients and their families should be told that the dose of Xenazine will be titrated up slowly to the dose that reduces chorea and is well tolerated. Sedation, akathisia, parkinsonism, depression, and difficulty swallowing may occur. Such symptoms should be reported immediately to the physician.
- 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 physician if the patient becomes pregnant or intends to become pregnant during therapy.
- Patients and their families should be advised to notify their physicians if the patient is breast-feeding an infant during therapy.
- Patients and their families should be advised to notify their physicians of all medications they are taking and to consult their physician before they start, stop, or change the dose of any medications.

Dosing Xenazine

- The dose of Xenazine should be individualized.
- Prescriptions may be written for either 12.5-mg or 25-mg tablets. The 25-mg tablets are scored.
- The starting dose should be 12.5 mg per day (12.5 mg 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 by 12.5 mg increments each week until satisfactory control of chorea is achieved or adverse events occur.

Initial Dosing Plan



- If a dose of 37.5 mg per day or greater is needed, it should be given in a 3-times-daily regimen.
- If daily doses of greater than 50 mg are necessary, patients should first be tested for the CYP2D6 gene to determine whether they are poor metabolizers (PMs) or extensive or intermediate metabolizers (EMs or IMs) of CYP2D6.
- For PMs, the maximum recommended single dose is 25 mg, and the maximum recommended daily dose is 50 mg.
- For IMs or EMs, the maximum recommended single dose is 37.5 mg, and the maximum recommended daily dose is 100 mg.
- Caution should be used when adding therapy with a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, or quinidine) to patients already receiving a stable dose of Xenazine; the daily dose of Xenazine should be halved.
- To initiate treatment with Xenazine in patients on a stable dose of a strong CYP2D6 inhibitor, the dosing recommendations for PMs of CYP2D6 should be followed.
- Before prescribing Xenazine talk to the patient and caregiver about what they should do if the patient misses a dose.
- Xenazine should be re-titrated after any treatment interruption lasting longer than 5 days.
- Xenazine is available in bottles of 112 tablets. Each prescription should be accompanied by a *Medication Guide*.

Please refer to the Xenazine Prescribing Information on pages 9-16.

Monitoring Therapy With Xenazine

Patients should be closely monitored, especially during titration to a maintenance dose. In addition to depression, suicidality and Neuroleptic Malignant Syndrome (see **The Most Important Information About Xenazine** on pages 1-3), the following are important adverse events that may occur with Xenazine:

- **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.

  In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with HD, akathisia was observed in 19% of 54 Xenazine-treated patients and none of 30 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.

- **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.

  In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with HD, symptoms suggestive of parkinsonism (ie, bradykinesia, hypertonia, and rigidity) were observed in 15% of 54 Xenazine-treated patients and none of 30 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.

- **Dysphagia.** Dysphagia is a component of HD. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. Because dysphagia may be associated with aspiration pneumonia, Xenazine and other drugs that reduce dopaminergic transmission should be used with caution in patients with HD at risk for aspiration pneumonia.

  In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with HD, dysphagia was observed in 4% of 54 Xenazine-treated patients and 3% of 30 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.

- **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.

  In a 12-week trial in patients with chorea associated with HD, sedation/somnolence was observed in 31% of 54 Xenazine-treated patients and in 3% of 30 placebo-treated patients. Sedation was the reason upward titration of Xenazine was stopped and/or the dose of Xenazine was decreased in 28% of 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, intolerable sedation occurred at doses that were lower than the efficacious doses.

- **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 the Prescribing Information on pages 9-16). The use of Xenazine should be avoided in combination with other drugs that are known to prolong QTc, including antipsychotic medications (eg, chlorpromazine, thioridazine, ziprasidone), antibiotics (eg, moxifloxacin), Class 1A (eg, quinidine, procainamide) and Class III (eg, amiodarone, sotalol) antiarrhythmic medications, or any other class of medications known to prolong the QTc interval.

- **Concomitant use of neuroleptic drugs.** Patients taking neuroleptic drugs (eg, haloperidol, chlorpromazine, risperidone, olanzapine) were excluded from clinical studies during the Xenazine development program. Adverse reactions associated with Xenazine, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists.
- **Interaction with alcohol and sedating drugs.** Patients should be advised that the concomitant use of alcohol or other sedating drugs might have additive effects and worsen sedation and somnolence (see **Information for Patients** in the Prescribing Information on pages 9-16).
- **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 increases. There is no known treatment for established TD, although the syndrome may remit partially or completely if the drug is withdrawn.
- **The most common adverse events** that may develop with use of Xenazine are sedation/somnolence, fatigue, insomnia, depression, anxiety, akathisia or restlessness, and nausea.

Treatment Interruption or Discontinuation of Therapy

Prescribers should periodically re-evaluate 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.

Discontinuation of Treatment

Treatment with Xenazine can be discontinued without tapering. Reemergence of chorea may occur within 12 to 18 hours after the last dose of Xenazine.

Please refer to the Xenazine Prescribing Information on pages 9-16.

Resumption of Treatment

Retitration of Xenazine should occur following any treatment interruption lasting longer than 5 days or a treatment interruption due to a change in the patient's medical condition or concomitant medications. If therapy with Xenazine is resumed, it should be retitrated according to the schedule described on page 5.

Xenazine Educational Materials

In addition to the Xenazine Prescribing Information (Package Insert), specialized educational materials will be available to aid prescribers, patients, and caregivers in familiarizing themselves with the risks and benefits of Xenazine therapy.

For Prescribers

- ***Prescribing Xenazine® (tetrabenazine) Tablets: A Healthcare Professional Guide***

  Describes the key risks and benefits of Xenazine therapy.

- ***Initial Dosing Plan***

  Highlights Xenazine titration through week three. After week three the prescriber should provide an individualized dosing plan for each patient; the prescriber should complete the card accordingly.

- **Xenazine Toll-Free Medical Information Line**

  Prestwick has a toll-free medical information line to provide healthcare professionals and patients with information about Xenazine (1-800-XXX-XXXX). This medical information line accepts and triages spontaneous adverse event reports for follow-up by Prestwick's pharmacovigilance program, as appropriate.

For Patients

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

- ***What You Need to Know About Xenazine (tetrabenazine): Patient/Caregiver Counseling Guide***

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

- ***Medication Guide***

  Provided to patients with every filled prescription of Xenazine, it provides information about titration, dosing, and monitoring for adverse events.

- ***Initial Dosing Plan***

  Provided to patients to provide information regarding their dosing.

Xenazine®
(tetrabenazine)
Tablets

Depression and Suicidality

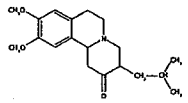
XENAZINE can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of XENAZINE must balance the risks of depression and suicidality with the clinical need for control of choreiform movements. Close observation 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; WARNINGS - Increased Risk of Depression and Suicidality, and PRECAUTIONS - Information for Patients).

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, maize starch, talc, and magnesium stearate. 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 tetrabenazine, or as a white non-scored tablet containing 12.5-mg of tetrabenazine.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The precise mechanism by which 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).

QTc Prolongation: The effect of a single 25 or 50 mg dose of tetrabenazine 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, tetrabenazine 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 tetrabenazine does not further increase the effect on the QTc interval. Effects at higher exposures to either tetrabenazine or its metabolites have not been evaluated. (See PRECAUTIONS - QTc Prolongation).

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.

Pharmacokinetics

Absorption and Distribution: 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 to 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 and β-HTBZ are subsequently metabolized to another major circulating metabolite, O-dealkylated-HTBZ, for which C_{max} is reached approximately 2 hours post-dosing.

The effects of food on the bioavailability of tetrabenazine 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.

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 and Excretion: α-HTBZ and β-HTBZ, major circulating metabolites, have half-lives of 4-8 hours and 2-4 hours, respectively. 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. β-HTBZ is O-dealkylated principally by CYP2D6.

After oral administration in humans, at least 19 metabolites of tetrabenazine have been identified. O-dealkylated HTBZ, α-HTBZ, and β-HTBZ are the major circulating metabolites, and they are subsequently metabolized to sulfate or glucuronide conjugates. CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP2E1 do not play a major role in metabolism of α-HTBZ or β-HTBZ based on *in vitro* studies.

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, CYP2C8, CYP2C9, CYP2C19, CYP2E1, or CYP3A. Their effect on CYP2B6 has not been evaluated. *In vitro* studies suggest that neither tetrabenazine nor its α- or β-HTBZ metabolites is 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*.

Excretion: After oral administration, tetrabenazine is extensively hepatically metabolized, and the metabolites are primarily renally eliminated. 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.

Special Populations

Pediatrics: The pharmacokinetics of tetrabenazine and its primary metabolites have not been studied in pediatric subjects.

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

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

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

Renal Disease: The effect of renal insufficiency on the pharmacokinetics of tetrabenazine and its primary metabolites has not been studied.

Liver Disease: 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 CONTRAINDICATIONS; PRECAUTIONS - Use in Patients with Concomitant Illness; and DOSAGE AND ADMINISTRATION).

CYP2D6 Poor Metabolizers

Although the pharmacokinetics of tetrabenazine 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 compared to subjects who express the enzyme (extensive metabolizers, EMs), with an increase similar to that observed in patients taking strong CYP2D6 inhibitors (3- and 9-fold, respectively). (see PRECAUTIONS - Drug Interactions and DOSAGE AND ADMINISTRATION). Patients should be genotyped for CYP2D6 prior to treatment with daily doses of tetrabenazine over 50 mg (see PRECAUTIONS - Laboratory Tests). Patients who are PMs should not be given daily doses greater than 50 mg. (see DOSAGE AND ADMINISTRATION)

Drug Interactions

α-HTBZ and β-HTBZ are metabolized principally by CYP2D6. A strong CYP2D6 inhibitor (paroxetine) markedly increases exposure to these metabolites (see PRECAUTIONS - Drug Interactions).

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

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 Huntington's disease (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/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 highly 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.

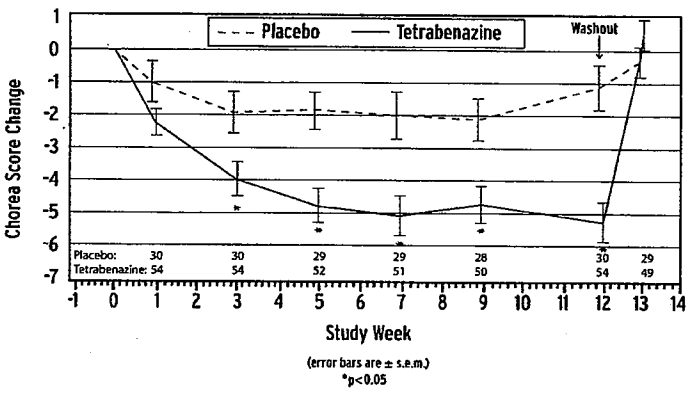
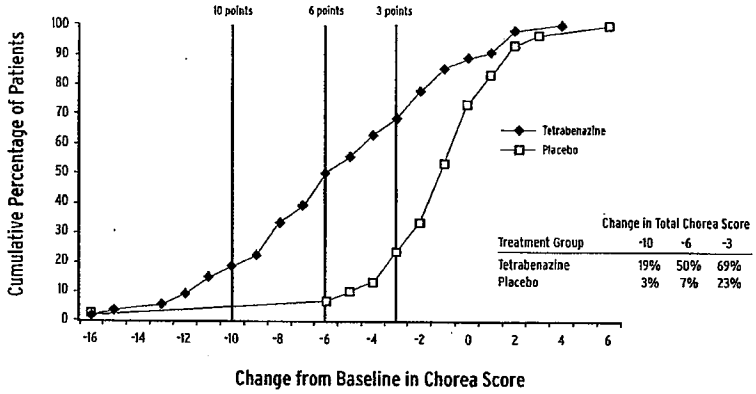


Figure 1. Mean ± s.e.m. Changes from Baseline in Total Chorea Score in 84 HD Subjects Treated with Tetrabenazine (n = 54) or Placebo (n = 30)

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 tetrabenazine-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 tetrabenazine-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.



Treatment Group	Change in Total Chorea Score -10	-6	-3
Tetrabenazine	19%	50%	69%
Placebo	3%	7%	23%

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 tetrabenazine 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 tetrabenazine 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).

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

XENAZINE is contraindicated in patients who are actively suicidal, or in patients with untreated or inadequately treated depression. XENAZINE is contraindicated in patients with impaired hepatic function. XENAZINE is contraindicated in patients taking monoamine oxidase inhibitors. Xenazine is contraindicated in patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting XENAZINE (see PRECAUTIONS–Drug Interactions).

WARNINGS

Huntington's disease is a progressive disorder characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time. Although XENAZINE has been shown to decrease the chorea of HD in a 12-week controlled trial, it was also shown to cause slight worsening in mood, cognition, rigidity, and functional capacity. Whether these effects persist, resolve, or worsen with continued treatment is unknown. 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 choreiform movements 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.

Need for Careful Dosing of Xenazine

Proper dosing of XENAZINE involves careful 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 well tolerated (see DOSAGE AND ADMINISTRATION). 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, consideration should be given to discontinuing tetrabenazine.

Doses above 50 mg should not be given without CYP2D6 genotyping (see WARNINGS: Laboratory Tests and PRECAUTIONS – Drug Interactions).

Risk of Depression and Suicidality

Patients with Huntington's disease are at increased risk for depression and suicidal ideation and behavior (suicidality). Tetrabenazine increases these risks. All patients treated with tetrabenazine should be observed closely for new or worsening depression or suicidality.

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 tetrabenazine 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 tetrabenazine (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%; over 25% of patients attempt suicide at some point in the 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. (See PRECAUTIONS - Information for Patients).

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

Caution should be exercised in treating patients with XENAZINE who have a history of depression or prior suicide attempts or ideation, as these patients may be at increased risk for suicidal behavior (See PRECAUTIONS - Information for Patients). Patients who are actively suicidal or with untreated or inadequately treated depression should not be treated with tetrabenazine (see CONTRAINDICATIONS)

Antidepressants that are strong CYP2D6 inhibitors significantly increase exposure to α- and β-HTBZ. (see PRECAUTIONS–Drug Interactions)

Laboratory Tests

Before patients are given a daily dose of greater than 50 mg, they should be tested for the CYP2D6 gene to determine whether they are poor metabolizers (PMs) or extensive or intermediate metabolizers (EMs or IMs). When a dose of tetrabenazine is given to PMs, exposure will be substantially higher (about 3-fold for α-HTBZ and 9-fold for β-HTBZ) than it would be in EMs. The dosage should therefore be adjusted according to a patient's CYP2D6 metabolizer status by limiting the dose to 50 mg in patients who are CYP2D6 poor metabolizers. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with tetrabenazine 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 diagnostic evaluation of patients with this syndrome is complicated. In arriving at the diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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

If the patient requires treatment with tetrabenazine after recovery from NMS, the potential reintroduction of therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

PRECAUTIONS

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.

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 tetrabenazine, 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. The latter symptom 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. XENAZINE and other drugs that reduce dopaminergic transmission should be used with caution in patients with Huntington's disease at risk for aspiration pneumonia.

Sedation and Somnolence

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

Patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, until they are on a maintenance dose of tetrabenazine and know how the drug affects them (see PRECAUTIONS - Information for Patients).

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- Pharmacodynamics). The use of XENAZINE should be avoided in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, 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.

Concomitant Use of Neuroleptic Drugs

Patients taking neuroleptic drugs (e.g., haloperidol, chlorpromazine, risperidone, olanzapine) were excluded from clinical studies during the tetrabenazine development program. Adverse reactions associated with tetrabenazine, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists.

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 Information for Patients).

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 tetrabenazine-treated patients (vs. none on placebo) in the 12-week controlled trial; blood pressure was not measured during these events. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension.

Hyperprolactinemia

Tetrabenazine 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 tetrabenazine 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 tetrabenazine 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 tetrabenazine.

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 tetrabenazine, 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 tetrabenazine 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.

Use in Patients With Concomitant Illness

Clinical experience with tetrabenazine in patients with systemic illnesses is limited. Caution is advised in using tetrabenazine in patients with a history of depression or suicidality (see WARNINGS - Risk of Depression and Suicide). Caution is also advised in using tetrabenazine in patients with diseases, conditions, or treatments that could cause depression or increased suicidality. Tetrabenazine is contraindicated in patients with hepatic impairment (See CONTRAINDICATIONS and CLINICAL PHARMACOLOGY - Special Populations) and in patients with untreated or inadequately treated depression or who are actively suicidal.

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

Binding to Melanin-Containing Tissues

Since tetrabenazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that tetrabenazine may cause toxicity in these tissues after extended use. Neither ophthalmologic nor microscopic examination of 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 tetrabenazine'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.

Information for Patients

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

Patients and their families should be told that XENAZINE may increase the risk of patients considering or attempting suicide. 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.

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.

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 may require dose reduction or tetrabenazine discontinuation.

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.

Patients and their families should be advised that alcohol may potentiate the sedation induced by XENAZINE.

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.

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.

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. Caution should be used when giving any strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine) to a patient already receiving a stable dose of tetrabenazine, and the daily dose of tetrabenazine should be halved (see DOSAGE AND ADMINISTRATION). The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline has not been evaluated. (See DOSAGE AND ADMINISTRATION)

Other Cytochrome P450 inhibitors: Based on *in vitro* studies, a clinically significant interaction between tetrabenazine and other P450 inhibitors (other than CYP2D6 inhibitors) is not likely. (See CLINICAL PHARMACOLOGY)

Reserpine: Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Caution should therefore be used when switching a patient from reserpine to XENAZINE. The physician should wait for chorea to re-emerge 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).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Lifetime carcinogenicity studies have not been conducted with tetrabenazine.

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.

Impairment of Fertility: Fertility and early embryonic development studies have not been conducted with tetrabenazine.

Pregnancy: Pregnancy Category C

Tetrabenazine had no clear effects on embryo-fetal development when administered to pregnant rats throughout the period of organogenesis at oral doses up to 30 mg/kg/day (or 3 times the maximum recommended human dose (MRHD) of 100 mg/day on a mg/m² basis). 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/m² basis).

When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. The no-effect dose for stillbirths and postnatal mortality was 0.5 times the MRHD on a mg/m² basis.

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. (See Information for Patients)

Labor and Delivery

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

Nursing Mothers

It is not known whether tetrabenazine 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 tetrabenazine, a decision should be made whether to discontinue nursing or to discontinue tetrabenazine, taking into account the importance of the drug to the mother.

Pediatric Use

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

ADVERSE REACTIONS

During its development, tetrabenazine was administered to 773 unique subjects and patients. The conditions and duration of exposure to tetrabenazine 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.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of adverse effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

In a randomized, 12-week, placebo-controlled clinical trial of HD subjects, adverse events (AEs) were more common in the tetrabenazine group than in the placebo group. Forty-nine of 54 (91%) patients who received XENAZINE experienced one or more AEs at any time during the study. The AEs 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). The number and percentage of the most commonly reported AEs that occurred at any time during the study in ≥4% of tetrabenazine-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 tetrabenazine group.

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

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

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

Table 2. Treatment Emergent Extrapyramidal Symptoms in Patients Treated with Tetrabenazine and 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.

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 ALT and AST laboratory values as compared to placebo.

Vital Signs

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Tetrabenazine is not a controlled substance.

Physical and Psychological Dependence

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 tetrabenazine has been marketed. Abrupt discontinuation of tetrabenazine from patients did not produce symptoms of withdrawal or a discontinuation syndrome; only symptoms of the original disease were observed to re emerge. 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 tetrabenazine misuse or abuse (such as development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

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

Overdose Management

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®).

DOSAGE AND ADMINISTRATION

In patients with chorea associated with Huntington's disease, proper dosing of XENAZINE involves careful 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 for chronic use that reduces chorea and is well tolerated. Doses above 100 mg/day are not recommended for any patient.

Dosing Recommendations up to 50 mg per day

The dose of XENAZINE should be individualized. 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, to allow the identification of a dose that reduces chorea and is well tolerated. 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 intolerable sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antidepressants).

Dosing Recommendations above 50 mg per day

Patients who appear to require doses greater than 50 mg per day should be genotyped for CYP2D6.

The dose of XENAZINE should be individualized.

For CYP2D6 Extensive and Intermediate Metabolizers (patients who express CYP2D6)

At doses above 50 mg per day, XENAZINE should be titrated up slowly at weekly intervals by 12.5 mg, to allow the identification of a dose that reduces chorea and is well tolerated. 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 intolerable sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antidepressants).

For CYP2D6 Poor Metabolizers (patients who do not express CYP2D6)

In patients who are CYP2D6 poor metabolizers, dosing is similar to EMs except that the recommended maximum single dose is 25 mg, and the maximum recommended daily dose is 50 mg.

Discontinuation of Treatment with XENAZINE

Treatment with XENAZINE can be discontinued without tapering. Re-emergence of chorea may occur within 12 to 18 hours after the last dose of tetrabenazine.

Resumption of Treatment

Following treatment interruption of greater than five (5) days or a treatment interruption occurring due to a change in the patient's medical condition or concomitant medications, XENAZINE therapy should be retitrated when resumed. For short-term treatment interruption of less than five (5) days, treatment can be resumed at the previous maintenance dose without titration.

SPECIAL POPULATIONS

Hepatically Impaired Patients: The use of XENAZINE in patients with liver disease is contraindicated (see CLINICAL PHARMACOLOGY - Hepatic Impairment and Special Populations under and CONTRAINDICATIONS and PRECAUTIONS - Use in Patients with Concomitant Illness).

Patients taking CYP2D6 Inhibitors

Caution should be used when adding a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine), to a patient already receiving a stable dose of tetrabenazine. In patients receiving co-administered strong CYP2D6 inhibitors, the daily dose of tetrabenazine should be halved. To initiate treatment with XENAZINE in patients on a stable dose of a strong CYP2D6 inhibitor, the dosing recommendations for the CYP2D6 poor metabolizers 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).

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 18722-001-01

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 18722-002-01

STORAGE

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

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Prestwick PHARMACEUTICALS

Prestwick Pharmaceuticals, Inc.
1825 K Street NW, Suite 1475
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MEDICATION GUIDE

XENAZINE (*ZEN-uh-zeen*)
(tetrabenazine)
Tablets

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.

What is the most important information I should know about Xenazine?

- **Xenazine may increase the chance of depression, suicidal thoughts, or suicidal actions in some patients.**
- You should not start taking Xenazine if you are depressed (have untreated depression or depression that is not well controlled by medicine) **or** have suicidal thoughts.
- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts or feelings. This is especially important when Xenazine is started and when the dose is changed.

Call the doctor right away if you become depressed or have any of the following symptoms, especially if they are new, worse, or worry you:

- You feel sad or have crying spells.
- You are no longer interested in seeing your friends or doing things you used to enjoy.
- You are sleeping a lot *more* or a lot *less* than usual.
- You feel unimportant.
- You feel guilty.
- You feel hopeless or helpless.
- You are more irritable, angry, or aggressive than usual.
- You are more or less hungry than usual or notice a big change in your body weight.
- You have trouble paying attention.
- You feel tired or sleepy all the time.
- You have thoughts about hurting yourself or ending your life.

What is Xenazine?

Xenazine is a medicine that is used to treat the involuntary movements (chorea) of Huntington's disease. Xenazine does not cure the cause of the involuntary movements, and it does not treat other symptoms of Huntington's disease, such as problems with thinking or emotions.

It is not known whether Xenazine is safe and effective in children.

Who should not take Xenazine?

Do not take Xenazine if you:

- are depressed or have thoughts of suicide. See "What is the most important information I should know about Xenazine?"
- have liver problems.

- are taking a monoamine oxidase inhibitor (MAOI) medicine. Ask your doctor or pharmacist if you are not sure.
- are taking reserpine. **Do not take medicines that contain reserpine (such as Serpalan® and Renese®-R) with Xenazine. If your doctor plans to switch you from taking reserpine to Xenazine, you must wait at least 20 days after your last dose of reserpine before you start taking Xenazine.**

What should I tell my doctor before taking Xenazine?

Tell your doctor about all your medical conditions, including if you:

- have emotional or mental problems (for example, depression, nervousness, anxiety, anger, agitation, psychosis, previous suicidal thoughts or suicide attempts).
- have liver disease.
- have any allergies. See the end of this Medication Guide for a complete list of the ingredients in Xenazine.
- have breast cancer or a history of breast cancer.
- have heart disease that is not stable, have heart failure or recently had a heart attack.
- have an irregular heart beat (cardiac arrhythmia).
- are pregnant or plan to become pregnant. It is not known if Xenazine can harm your unborn baby.
- are breast-feeding. It is not known if Xenazine passes into breast milk.

Tell your doctor about all the medicines you take, including prescription medicines and nonprescription medicines, vitamins and herbal products. Using Xenazine with certain other medicines may cause serious side effects. **Do not start <u>any</u> new medicines while taking Xenazine without talking to your doctor first.**

How should I take Xenazine?

- Xenazine is a tablet that you take by mouth.
- **Take Xenazine exactly as prescribed by your doctor.**
- You may take Xenazine with or without food.
- Your doctor will increase your dose of Xenazine each week for several weeks, until you and your doctor find the best dose for you.
- If you stop taking Xenazine or miss a dose, your involuntary movements may return or worsen in 12 to 18 hours after the last dose.
- Before starting Xenazine, you should talk to your health care 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.
- Tell your doctor if you stop taking Xenazine for more than 5 days. **Do not take another dose until you talk to your doctor.**
- **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 it is safe for you.**

What should I avoid while taking Xenazine?

Sleepiness (sedation) is a common side effect of Xenazine. While taking Xenazine **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.

What are the possible side effects of Xenazine?

Xenazine can cause serious side effects, including:

- **Depression, suicidal thoughts, or actions.** See "What is the most important information I should know about Xenazine?"
- **Neuroleptic Malignant Syndrome (NMS).** Call your doctor right away and go to the nearest emergency room if you develop these signs and symptoms that do not have another obvious cause:
  - high fever
  - stiff muscles
  - problems thinking
  - very fast or uneven heartbeat
  - increased sweating
- **Parkinsonism.** Symptoms of Parkinsonism include: slight shaking, body stiffness, trouble moving or keeping your balance.
- **Restlessness.** You may get a condition where you feel a strong urge to move. This is called akathisia.
- **Trouble swallowing.** Xenazine 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.
- **Irregular heartbeat.** Xenazine increases your chance of having certain changes in the electrical activity in your heart which 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 due to blood pressure changes when you change position (orthostatic hypotension).** Change positions slowly from lying down to sitting up and from sitting up to standing when taking Xenazine. Tell your doctor right away if you get dizzy or faint while taking Xenazine. Your doctor may need to watch your blood pressure closely.
- **Tardive dyskinesia (TD).** TD is a condition where there is repeated facial grimacing that cannot be controlled, sticking out of the tongue, smacking of the lips, puckering and pursing of the lips, and rapid eye blinking. Xenazine works like other drugs that can cause TD. If you get TD with Xenazine, it is possible that the TD will not go away.

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.

Call your doctor for medical advice about side effects. You may report side effects to the Food and Drug Administration (FDA) at 1-800-FDA-1088.

General information about Xenazine

Xenazine contains the active ingredient tetrabenazine. It also contains these inactive ingredients: lactose, maize starch, talc, and magnesium stearate. The 25-mg tablet, which is pale yellow, also contains yellow iron oxide.

Medicines are sometimes prescribed for conditions that are not listed in a Medication Guide. Do not use Xenazine for a condition for which it was not prescribed. Do not give Xenazine to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Xenazine. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Xenazine that is written for healthcare professionals. You can also call the Xenazine Hotline at **1-800-XXX-XXXX or visit www.------.com.**

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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1825 K Street NW, Suite 1475
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Prescribing Xenazine® (tetrabenazine) Tablets

A Healthcare Professional Guide

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Please refer to the Xenazine Prescribing Information on pages 9-16.

INITIAL DOSING PLAN | Xenazine® (tetrabenazine) Tablets

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						Morning
Afternoon			12.5 mg						Afternoon
Evening		12.5 mg	12.5 mg						Evening
Total Daily Dose	12.5 mg	25 mg	37.5 mg						Total Daily Dose

How Should I Take Xenazine?

Xenazine is a tablet you take by mouth. You may take it with or without food. There are 2 strengths of Xenazine:

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

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.

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.
- 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.
- 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.
- For most patients, the maximum recommended daily dose is 100 mg. For some patients, the maximum daily dose may be 50 mg.

Skipping or Stopping Xenazine

- Before starting Xenazine, you should talk to your health care 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 in 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 toll-free medical information line any time you have questions or worries: **1-800-XXX-XXXX**
For more information about Xenazine visit our web site at **www.xxxxxxxx.com**

What You Need to Know About Xenazine® (tetrabenazine)

Patient/Caregiver Counseling Guide

NOTE TO PRESCRIBER: Please provide this guide to your patient or your patient's caregiver.

What Is the Most Important Information About Xenazine?

- Xenazine (*ZEN-uh-zeen*) is a prescription medicine to treat involuntary movements of Huntington's disease. Involuntary movements, also called chorea, are a major feature of Huntington's disease.
- 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 well 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 Huntington's disease, 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 Huntington's disease 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 Huntington's disease. The chance that these changes in mood or behavior may occur is increased in patients who are taking Xenazine. All patients treated with Xenazine should be observed closely for new or worsening depression, thoughts of suicide, or attempted suicide. This is especially important when starting therapy with Xenazine or when changing the dose of Xenazine.

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

Please see Xenazine *Medication Guide* on pages 10-13.

What Are the Signs You May be Depressed or At Risk for Suicide?

- You feel sad or have crying spells.
- You are no longer interested in seeing your friends or doing things you used to enjoy.
- You are sleeping a lot *more* or a lot *less* than usual.
- You feel unimportant.
- You feel guilty.
- You feel hopeless or helpless.
- You are more irritable, angry, or aggressive than usual.
- You are *more* or *less* hungry than usual or notice a big change in your body weight.
- You have trouble paying attention.
- You feel tired or sleepy all the time.
- You have thoughts about hurting yourself or ending your life.

What Should I Do If I Have These Signs?

Call your doctor right away if you become depressed or develop any of the signs listed above. Talk to your doctor about it, especially if your feelings are new, they have become worse, or you are worried about them.

Please see Xenazine *Medication Guide* on pages 10-13.

What Is Xenazine® (tetrabenazine)?

Xenazine is a medication taken by mouth to treat involuntary movements of Huntington's disease. Involuntary movements, also called chorea, are a major feature of Huntington's disease. 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 Huntington's disease, such as problems with thinking or emotions.

How Does Xenazine Work?

Doctors are not sure what causes chorea. Overactivity of a chemical in the brain, dopamine (*DOH-puh-meen*), may cause it.

Doctors are not sure how Xenazine reduces 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. You may become more depressed while taking Xenazine.
- Medicine you take for depression has not helped enough.
- You think or talk about harming or killing yourself (suicide). You may become more likely to think about ending your life while taking Xenazine.
- You have liver problems.
- You take a monoamine oxidase (MAO) inhibitor, or reserpine, or medicine that contains reserpine.
  - Examples of MAO inhibitors are Nardil® (phenelzine), Eldepryl® (selegiline), and Parnate® (tranylcypromine).
  - Examples of medicines that contain reserpine are Serpalan® or Renese®-R. You must stop taking reserpine for at least 20 days before you begin therapy with Xenazine.
- If you are not sure if you are taking an MAO inhibitor or a medicine that contains reserpine, ask your doctor or pharmacist.

Please see Xenazine *Medication Guide* on pages 10-13.

Before You Start to Take Xenazine

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 you doctor if you have any of these health conditions:

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

Physical conditions

- Liver problems.
- Allergies to any of the ingredients in Xenazine Tablets.
  Xenazine contains the active ingredient tetrabenazine. It also contains these inactive ingredients: lactose, maize starch, talc, and magnesium stearate. The 25-mg tablet, which is pale yellow, also contains yellow iron oxide.
- 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.
- You have an irregular heart beat (cardiac arrhythmia).
- You are pregnant or plan to become pregnant.
  The effect of Xenazine on an unborn baby is not known.
- You are nursing a baby.
  It is not known if Xenazine passes into breast milk.

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 drugs
- Change the dose of any of your medicines
- Stop taking any of your medicines

How Should I Take Xenazine?

Xenazine is a tablet you take by mouth. You may take it with or without food. There are 2 strengths of Xenazine:

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

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.

Skipping or Stopping Xenazine

- Before starting Xenazine, you should talk to your health care provider 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 in 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.

Please see Xenazine *Medication Guide* on pages 10-13.

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.
- 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.
- 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.
- For most patients, the maximum recommended daily dose is 100 mg. For some patients, the maximum daily dose may be 50 mg.

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.

Please see Xenazine *Medication Guide* on pages 10-13.

Monitor Your Treatment With Xenazine

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

The Most Serious Side Effects that May Develop With Xenazine

- **Depression or thoughts of suicide.** Xenazine may worsen a patient's mood or ability to think clearly. It may be difficult to tell if these side effects are due to Huntington's disease 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 the section *What Is the Most Important Information About Xenazine?*)

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.

  The signs of NMS are

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

  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.

- **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 Huntington's disease, it may be difficult to tell if this side effect is due to Huntington's disease or Xenazine.

  If you develop the signs of parkinsonism, your doctor may reduce your dose of Xenazine or stop therapy 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 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.
- **Tardive dyskinesia (TD).** 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.
- **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 (See the section *Tell Your Doctor Which Medications You Are Taking*).
- **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.

Please see Xenazine *Medication Guide* on pages 10-13.

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.

What Should I Do If I Have a Side Effect With Xenazine?

Call your doctor if you have any of the side effects listed above or any other possible side effects not listed above. 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.

Talk to Your Doctor

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.

Please see Xenazine *Medication Guide* on pages 10-13.

MEDICATION GUIDE

XENAZINE (*ZEN-uh-zeen*)
(tetrabenazine)
Tablets

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.

What is the most important information I should know about Xenazine?

- **Xenazine may increase the chance of depression, suicidal thoughts, or suicidal actions in some patients.**
- You should not start taking Xenazine if you are depressed (have untreated depression or depression that is not well controlled by medicine) **or** have suicidal thoughts.
- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts or feelings. This is especially important when Xenazine is started and when the dose is changed.

Call the doctor right away if you become depressed or have any of the following symptoms, especially if they are new, worse, or worry you:

- You feel sad or have crying spells.
- You are no longer interested in seeing your friends or doing things you used to enjoy.
- You are sleeping a lot *more* or a lot *less* than usual.
- You feel unimportant.
- You feel guilty.
- You feel hopeless or helpless.
- You are more irritable, angry, or aggressive than usual.
- You are more or less hungry than usual or notice a big change in your body weight.
- You have trouble paying attention.
- You feel tired or sleepy all the time.
- You have thoughts about hurting yourself or ending your life.

What is Xenazine?

Xenazine is a medicine that is used to treat the involuntary movements (chorea) of Huntington's disease. Xenazine does not cure the cause of the involuntary movements, and it does not treat other symptoms of Huntington's disease, such as problems with thinking or emotions.

It is not known whether Xenazine is safe and effective in children.

Who should not take Xenazine?

Do not take Xenazine if you:

- are depressed or have thoughts of suicide. See "What is the most important information I should know about Xenazine?"
- have liver problems.

- are taking a monoamine oxidase inhibitor (MAOI) medicine. Ask your doctor or pharmacist if you are not sure.
- are taking reserpine. **Do not take medicines that contain reserpine (such as Serpalan® and Renese®-R) with Xenazine. If your doctor plans to switch you from taking reserpine to Xenazine, you must wait at least 20 days after your last dose of reserpine before you start taking Xenazine.**

What should I tell my doctor before taking Xenazine?

Tell your doctor about all your medical conditions, including if you:

- have emotional or mental problems (for example, depression, nervousness, anxiety, anger, agitation, psychosis, previous suicidal thoughts or suicide attempts).
- have liver disease.
- have any allergies. See the end of this Medication Guide for a complete list of the ingredients in Xenazine.
- have breast cancer or a history of breast cancer.
- have heart disease that is not stable, have heart failure or recently had a heart attack.
- have an irregular heart beat (cardiac arrhythmia).
- are pregnant or plan to become pregnant. It is not known if Xenazine can harm your unborn baby.
- are breast-feeding. It is not known if Xenazine passes into breast milk.

Tell your doctor about all the medicines you take, including prescription medicines and nonprescription medicines, vitamins and herbal products. Using Xenazine with certain other medicines may cause serious side effects. **Do not start <u>any</u> new medicines while taking Xenazine without talking to your doctor first.**

How should I take Xenazine?

- Xenazine is a tablet that you take by mouth.
- **Take Xenazine exactly as prescribed by your doctor.**
- You may take Xenazine with or without food.
- Your doctor will increase your dose of Xenazine each week for several weeks, until you and your doctor find the best dose for you.
- If you stop taking Xenazine or miss a dose, your involuntary movements may return or worsen in 12 to 18 hours after the last dose.
- Before starting Xenazine, you should talk to your health care 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.
- Tell your doctor if you stop taking Xenazine for more than 5 days. **Do not take another dose until you talk to your doctor.**
- **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 it is safe for you.**

What should I avoid while taking Xenazine?

Sleepiness (sedation) is a common side effect of Xenazine. While taking Xenazine **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.

What are the possible side effects of Xenazine?

Xenazine can cause serious side effects, including:

- **Depression, suicidal thoughts, or actions.** See "What is the most important information I should know about Xenazine?"
- **Neuroleptic Malignant Syndrome (NMS).** Call your doctor right away and go to the nearest emergency room if you develop these signs and symptoms that do not have another obvious cause:
  - high fever
  - stiff muscles
  - problems thinking
  - very fast or uneven heartbeat
  - increased sweating
- **Parkinsonism.** Symptoms of Parkinsonism include: slight shaking, body stiffness, trouble moving or keeping your balance.
- **Restlessness.** You may get a condition where you feel a strong urge to move. This is called akathisia.
- **Trouble swallowing.** Xenazine 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.
- **Irregular heartbeat.** Xenazine increases your chance of having certain changes in the electrical activity in your heart which 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 due to blood pressure changes when you change position (orthostatic hypotension).** Change positions slowly from lying down to sitting up and from sitting up to standing when taking Xenazine. Tell your doctor right away if you get dizzy or faint while taking Xenazine. Your doctor may need to watch your blood pressure closely.
- **Tardive dyskinesia (TD).** TD is a condition where there is repeated facial grimacing that cannot be controlled, sticking out of the tongue, smacking of the lips, puckering and pursing of the lips, and rapid eye blinking. Xenazine works like other drugs that can cause TD. If you get TD with Xenazine, it is possible that the TD will not go away.

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.

Call your doctor for medical advice about side effects. You may report side effects to the Food and Drug Administration (FDA) at 1-800-FDA-1088.

General Information about Xenazine

Xenazine contains the active ingredient tetrabenazine. It also contains these inactive ingredients: lactose, maize starch, talc, and magnesium stearate. The 25-mg tablet, which is pale yellow, also contains yellow iron oxide.

Medicines are sometimes prescribed for conditions that are not listed in a Medication Guide. Do not use Xenazine for a condition for which it was not prescribed. Do not give Xenazine to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Xenazine. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Xenazine that is written for healthcare professionals. You can also call the Xenazine Hotline at **1-800-XXX-XXXX or visit www.------.com.**

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Understanding Your Therapy With Xenazine® (tetrabenazine)

You will be given 2 guides to help you understand your therapy with Xenazine. The first is this guide, *What You Need to Know About Xenazine® (tetrabenazine)*, which tells you about your treatment with Xenazine.

You will also be given the *Xenazine® (tetrabenazine) Medication Guide* every time your prescription is filled. The medication guide is a short version of this guide. You will also receive an *Initial Dosing Plan*.

For more information on your treatment with Xenazine, call the Xenazine toll-free medical information line at 1-800-XXX-XXXX or visit www.----.com on the Internet. All this information does not take the place of talking to your doctor about your medical condition or your treatment.

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 Xenazine toll-free medical information line: 1-800-XXX-XXXX

Do You Have Questions About Your Treatment With Xenazine?
Call the Xenazine toll-free medical information line any time you have questions or worries.
1-800-XXX-XXXX
For more information about Xenazine, visit our web site at www.xxxxxxxx.com

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
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