Xenazine®
(tetrabenazine)
Tablets

Depression and Suicidality

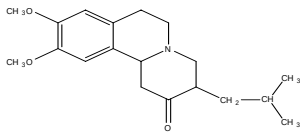
XENAZINE can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of XENAZINE must balance the risks of depression and suicidality with the clinical need for control of choreiform movements. Close observation 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

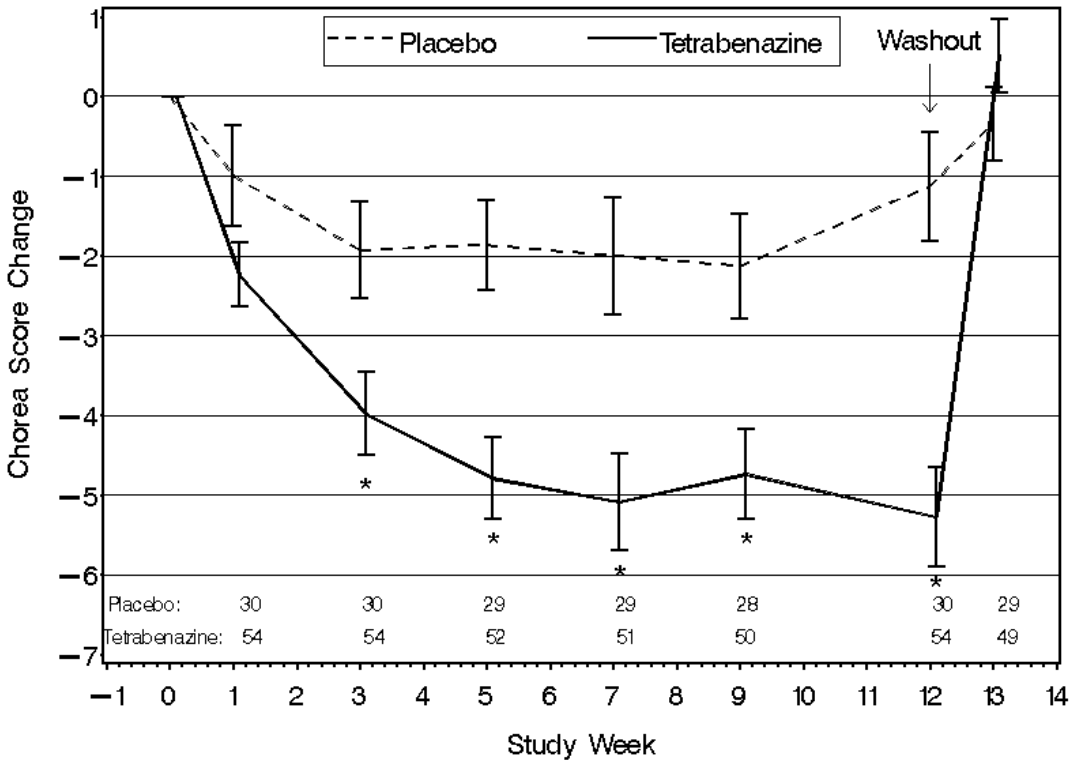
Study 1

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 12.5mg/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.



(error bars are ± s.e.m.)

*p<0.05

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.

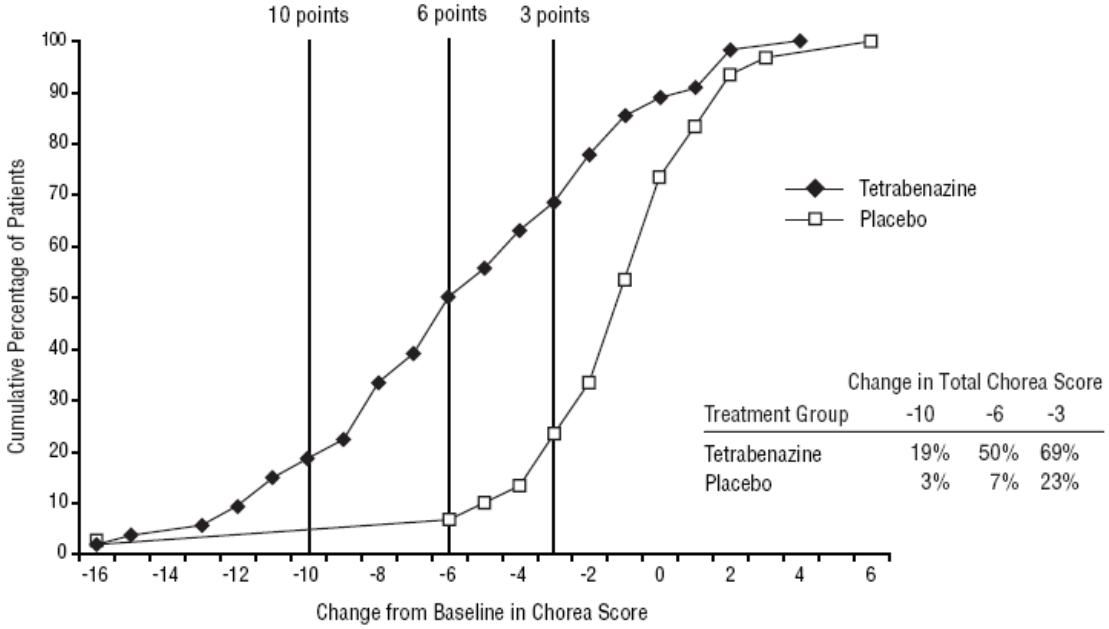


Figure 2. Cumulative Percentage of Patients with Specified Changes from Baseline in Total Chorea Score. The Percentages of Randomized Patients within each treatment group who completed Study 1 were: Placebo 97%, Tetrabenazine 91%.

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 therap**y.**

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/m^2 basis). Tetrabenazine had no effects on embryo-fetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day (or 12 times the MRHD on a mg/m^2 basis).

When tetrabenazine was administered to female rats (doses of 5, 15, and 30 mg/kg/day) from the beginning of organogenesis through the lactation period, an increase in stillbirths and offspring

postnatal mortality was observed at 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. The no-effect dose for stillbirths and postnatal mortality was 0.5 times the MRHD on a mg/m^2 basis.

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 T**reated 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 T**reated with Tetrabenazine and with a Greater Frequency than Placebo** in the 12-Week, Double-Blind, Placebo-Controlled Trial of XENAZINE

	Patients (%) reporting event	
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 1g. AEs associated with tetrabenazine overdose included acute dystonia, oculogryic 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 25º C (77º F); excursions permitted to 15-30ºC (59-86º F) [see USP Controlled Room Temperature].

Distributed by:

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