Your next move could help hers

**Indications and Usage:**
XENAZINE is indicated for the treatment of chorea associated with Huntington’s disease.

**Important Safety Information:**

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Xenazine® is a registered trademark of Biovail Laboratories International (Barbados) SRL

---

**The only FDA-approved treatment for chorea associated with Huntington’s disease**

Click here to learn more about Xenazine
Or visit www.XenazineUSA.com

---

For more information about Xenazine, please see Brief Summary of Prescribing Information on adjacent pages.

©2012 Lundbeck. All rights reserved. XZN327W 5/2012
WARNINGS AND PRECAUTIONS

Clinical Worsening and Adverse Effects

Huntington’s disease is a progressive disorder characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time. If a 12-week controlled trial, XENAZINE was also shown to cause slight worsening in mood, cognition, rigidity, and functional capacity. Whether these effects persist, resolve, or worsen with continued treatment is unknown. Therefore, proper use of the drug requires attention to all facets of the underlying disease process over time.

Prescribers should periodically re-evaluate the need for XENAZINE in their patients by assessing the beneficial effect on chorea and possible adverse effects, including depression, worsening of chorea, dyskinesia, parkinsonism, dystonia, sedation, somnolence, akathisia, akinesia, restlessness, and dizziness. 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 may improve over time, decreasing the need for XENAZINE.

Dosing of XENAZINE

Proper dosing of XENAZINE involves titration of therapy to determine an individualized dose for each patient. When first prescribed, XENAZINE therapy should be titrated slowly over several weeks to identify a dose of XENAZINE that reduces chorea and is tolerated. XENAZINE can be administered without regard to food.

Individualization of Dose

The dose of XENAZINE should be individualized.

Dosage Recommendations Up to 50 mg per day

The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given at 12.5 mg twice a day. This should be titrated up slowly at weekly intervals by 12.5 mg. If the Identification of a tolerated dose that reduces chorea if a dose of 37.5 to 50 mg per day is reached, it should be given in three a three times a day regimen. The maximum recommended single dose is 25 mg. If adverse effects such as akathisia, restlessness, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse event does not resolve, consideration should be given to withdrawing XENAZINE treatment or initiating other specific treatment (e.g., antipsychotics).

Dosage Recommendations Above 50 mg per day

Patients who require doses of XENAZINE greater than 50 mg per day should be tapered first and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized according to their status as PMs or EMs.

Extensive and Intermediate CYP2D6 Metabolizers

Patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized according to their status as PMs or EMs.

Strong CYP2D6 Inhibitors

Medications that are strong CYP2D6 inhibitors such as quinidine or antidepressants (e.g., Fluoxetine, paroxetine) significantly increase the exposure to α-HTBZ and β-HTBZ. Therefore, the total dose of XENAZINE should not exceed a maximum of 50 mg and the maximum recommended single dose should not exceed 25 mg.

Patients with Hepatic Impairment

Because the safety and efficacy of the increased exposure to XENAZINE and other circulating metabolites are unknown, it is not possible to adjust the dosage of XENAZINE in hepatic impairment to ensure safe use. Therefore, XENAZINE is contraindicated in patients with hepatic impairment.

Discontinuation of Treatment

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

Resumption of Treatment

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

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 (MAOIs). XENAZINE should not be used in combination with an MAO or within a minimum of 14 days of discontinuing therapy with an MAO. XENAZINE is contraindicated in patients taking reserpine. At least 20 days should elapse after stopping reserpine before starting XENAZINE.

WARNINGs AND PRoCAUTIONs

Clinical Worsening and Adverse Effects

Huntington’s disease is a progressive disorder characterized by changes in mood, cognition, chorea, rigidity, and functional capacity over time. For the first controlled trial, XENAZINE was shown to cause slight worsening in mood, cognition, rigidity, and functional capacity.
The clinical relevance of XENAZINE’s binding to melanin-containing tissues is unknown. Although there are no microscopic examination of the eye was conducted in the chronic toxicity study in dogs. Ophthalmologic monitoring, since XENAZINE or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. Patients with these diagnoses were excluded from premarketing clinical trials. XENAZINE has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Depression and Suicidality Clinical experience with XENAZINE in patients with systemic illnesses is limited. Physicians should be aware of the possible risk of tardive dyskinesia. If signs and symptoms of TD appear in a patient treated with XENAZINE, the drug discontinuation should be considered.

**ADVERSE REACTIONS**

**Commonly Observed Adverse Reactions in Controlled Clinical Trials**

<table>
<thead>
<tr>
<th>Body System</th>
<th>AE Term</th>
<th>XENAZINE n = 54 (%)</th>
<th>Placebo n = 30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSYCHIATRIC DISORDERS</strong></td>
<td>Sedation/somnolence</td>
<td>11 (21)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>12 (23)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>10 (19)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>7 (13)</td>
<td>6 (20)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>3 (6)</td>
<td>3 (10)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>2 (4)</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>3 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal System Disorders</td>
<td>Nausea</td>
<td>7 (13)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>6 (11)</td>
<td>2 (7)</td>
</tr>
<tr>
<td></td>
<td>Bowel Dysfunction</td>
<td>3 (6)</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td><strong>RESPIRATORY SYSTEM DISORDERS</strong></td>
<td>Shortness of breath</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachypnea</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Case escalation was discontinued in dosage of study drug was reduced because of m Of patients randomized to XENAZINE. All these consisted of sedation (15), akathisia (7), parkinsonism (6), depression (3), anxiety (3), fatigue (1) and subsidence. Some patients had more than one AE and, therefore, counted more than once.

**Adverse Reactions Due to Extrapyramidal Symptoms (EPS)** The following table shows the incidence of EPS reported in patients treated with XENAZINE occurring with a Greater Frequency Than Placebo in the 12-Week, Double-Blind, Placebo-Controlled Trial of XENAZINE

<table>
<thead>
<tr>
<th>Event</th>
<th>XENAZINE n = 54</th>
<th>Placebo n = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>10 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Extrapyramidal event</td>
<td>8 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Any extrapyramidal event</td>
<td>10 (19)</td>
<td>0</td>
</tr>
</tbody>
</table>
Laboratory Tests
No clinically significant changes in laboratory parameters were reported in clinical trials with XENAZINE. In controlled clinical trials, XENAZINE caused a small mean increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), laboratory values as compared to placebo.

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

DRUG INTERACTIONS
Strong CYP2D6 Inhibitors
In vitro studies indicate that (-)-HTBZ and (+)-HTBZ are substrates for CYP2D6. Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) in patients maintained on a stable dose of XENAZINE. The daily oral dose of XENAZINE should not exceed 50 mg per day and the maximum single oral dose of XENAZINE should not exceed 25 mg in patients taking strong CYP2D6 inhibitors.

Reserpine
Reserpine levels increased in Wistar and the duration of its effect is several days. Prescriptions should wait for 2-3 weeks before administering XENAZINE to avoid cross-sensitivity and major depletion of catecholamines in the brain. At least 21-days should elapse before stopping reserpine before starting XENAZINE. XENAZINE and reserpine should not be used concomitantly.

Monoamine Oxidase Inhibitors (MAOIs)
XENAZINE should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI.

Alcohol
Concurrent use of alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

Drugs that Cause QTC Prolongation
Since XENAZINE causes a small increase in QTC prolongation (about 8 ms), the concurrent use with other drugs that are known to cause QTC prolongation should be avoided including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, phenothiazines, and pimozide), 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 or sudden death in association with the use of drugs that prolong the QTC interval, including (1) florbetapir, (2) haloperidol, (3) haloperidol type antagonists, (4) concurrent use of other drugs that prolong the QTC interval, and (5) presence of congenital prolongation of the QTC interval.

Neuroleptic Drugs
Adverse reactions associated with XENAZINE, such as QTC prolongation, HVS, and extrapyramidal disorders, may be exaggerated by concurrent use of dopamine antagonists, including antipsychotics (e.g., chlorpromazine, haloperidol, thioridazine, fluphenazine).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. XENAZINE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Toremifene had no effects on embryonic-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 of 15 mg/day on a mg/m² basis). Toremifene had effects on embryonic-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 maximum recommended human dose of 30 mg/kg on a mg/m² basis). Because neither nor rat nor rabbit exposed to toremifene produce 9-desmethyl-clomiphene, these studies may not have adequately addressed the potential effects of toremifene on embryonic-fetal development in humans.

When toremifene was administered to female rats (doses of 5, 15, and 30 mg/kg) from the beginning of pregnancy through lactation, an increase in stillbirths and offspring postnatal mortality was observed at oral doses of 5 and 15 mg/kg (or 1.5 and 3 times the maximum recommended human dose on a mg/m² basis). Because rat liver showed that toremifene does not produce 9-desmethyl-beta-CLMTX (a major human metabolite), this study may not have adequately assessed the potential effects of toremifene on the offspring of women exposed in utero and in lactation.

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

Nursing Mothers
It is not known whether XENAZINE or its metabolites are excreted in human milk. Since many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from XENAZINE, a decision should be made whether to discontinue nursing or to discontinue XENAZINE, taking into account the importance of the drug to the mother.

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

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

Use in Patients with Hepatic Disease
The use of XENAZINE in patients with liver disease is contraindicated.

Use in Patients with Depression and Suicidality
Patients with HD are at increased risk for depression, suicidal ideation and behavior (suicidality), and XENAZINE increases these risks. XENAZINE is contraindicated in patients with uncontrolled or inadequately treated diabetes or who are actively suicidal. XENAZINE may increase the risk of depression or suicidality in patients with a history of depression or suicidal behavior or in patients with diseases, conditions, or treatments that cause depression or suicidality.

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

Use in Poor in Extensive CYP2D6 Metabolizers
Patients who require doses of XENAZINE greater than 50 mg per day should be first tested and genotyped to determine if they are poor (PMs) or extensive metabolizers (EMs) by their ability to express the drug-metabolizing enzyme, CYP2D6. The dose of XENAZINE should then be individualized according to their status as either poor (PMs) or extensive metabolizers (EMs).

Poor Metabolizers
Poor CYP2D6 metabolizers (PMs) will have substantially higher levels of exposure to the primary metabolites 9-desmethyl-XENAZINE and (+)-HTBZ, compared to EMs. The dose should, therefore, be adjusted according to a patient’s CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose not to exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs.

Use in Patients with Renal Disease
The effects of renal insufficiency in the pharmacokinetics of XENAZINE and its primary metabolites have not been formally studied.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
XENAZINE is not a controlled substance.

Clinical Trials
Clinical trials did not reveal any tendency for drug seeking behavior, though these observations were not systematic.

Abuse
Abuse has not been reported from the postmarketing experience in countries where XENAZINE has been marketed.

Use in Patients with CNS-Active Drug
XENAZINE should be used cautiously in patients with a history of drug abuse or alcoholism.

Management of Overdose
Treatment should consist of those general measures employed in the management of overdose with any CNS-active drug. General supportive and symptomatic measures are recommended. Carbohydrate and viral signs should be monitored. In managing overdose, the possibility of multiple drug involvement should always be considered. The physician should consider contacting a poison control center or the treatment of any overdose. Telephone numbers for poison control centers in the United States are listed in the yellow pages under “Toxin Reference” (PDR).

OVERDOSAGE

Human Experience
Three episodes of overdose occurred in the open-label trials performed in support of registration. Eight cases of overdose with XENAZINE have been reported in the literature. The dose of XENAZINE in these patients ranged from 150 mg to 1 g. Adverse reactions associated with XENAZINE overdose included acute dyskinesia, scoliotic crisis, massive and vomiting, abdominal pain, hypotension, electrocardiogram changes, bradycardia, arrhythmias, seizures, and other serious complications.

Management of Overdose
Treatment should include those general measures employed in the management of overdose with any CNS-active drug. General supportive and symptomatic measures are recommended. Carbohydrate and viral signs should be monitored. In managing overdose, the possibility of multiple drug involvement should always be considered. The physician should consider contacting a poison control center or the treatment of any overdose. Telephone numbers for poison control centers are listed in the yellow pages under “Toxin Reference” (PDR).

HOW SUPPLIED/STORAGE AND HANDLING

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

- The 25 mg XENAZINE tablets are white, cylindrical biplanar tablets with beveled edges, non-scored, embossed on one side with “CL” and “12.5”.
- The 25 mg XENAZINE tablets are white, cylindrical biplanar tablets with beveled edges, non-scored, embossed on one side with “CL” and “25”.

Bottles of 112: NDC 67386-421-01

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

Manufactured by:
Depalma-Fontaine SAS
Rue des Prés Potets
21213 Fontaine-lès-Dijon
France

For:

Xenazine® is a registered trademark of Biovail Laboratories International (Barbados) SRL

Revised May 2011