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Tetra benzazine Tablets
12.5 mg and 25 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use TETRA BENZAZINE safely and effectively. See full prescribing information for TETRA BENZAZINE TABLETS.

TETRA BENZAZINE tablets, for oral use Initial U.S. Approval: 2008

- WARNING: DEPRESSION AND SUICIDALITY**
See full prescribing information for complete boxed warning.
- Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (5.7)
 - Balance risks of depression and suicidality with the clinical need for control of chorea when considering the use of tetra benzazine tablets (5.1)
 - Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.2)
 - Inform patients, caregivers and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician (5.4)
 - Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.2)
 - Tetra benzazine tablets are contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression (4, 5.2)

INDICATIONS AND USAGE
Tetra benzazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease (1)

- DOSSAGE AND ADMINISTRATION**
- Individualization of dose with careful weekly titration is required. The 1st week's starting dose is 12.5 mg daily, 2nd week, 25 mg (12.5 mg twice daily), then slowly titrate at weekly intervals by 12.5 mg up to a tolerated dose that reduces chorea (2, 1, 2, 2)
 - Doses of 37.5 mg and up to 50 mg per day should be administered in three divided doses per day with a maximum recommended single dose not to exceed 25 mg (2, 2)
 - Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM) (2, 2, 3)
 - Maximum daily dose is PMs: 50 mg with a maximum single dose of 25 mg (2, 2)
 - Maximum daily dose is EMs and intermediate metabolizers (IMs): 100 mg with a maximum single dose of 37.5 mg (2, 2)
 - If serious adverse reactions occur titration should be stopped and the dose should be reduced. If adverse reaction(s) do not resolve, consider withdrawal of tetra benzazine tablets (2, 2)

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FULL PRESCRIBING INFORMATION

WARNING: DEPRESSION AND SUICIDALITY

Tetra benzazine tablets can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of tetra benzazine tablets must balance the risks of depression and suicidality with the clinical need for control of chorea. 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. Tetra benzazine tablets are contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression (see Contraindications (4), Warnings and Precautions (5.2)).

- INDICATIONS AND USAGE**

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

- DOSSAGE AND ADMINISTRATION**

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

Individualization of Dose
The dose of tetra benzazine tablets should be individualized.

Dosing Recommendations Up to 50 mg per day
The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day as 12.5 mg twice a day. Tetra benzazine tablets should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. 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 reactions such as alkalemia, restlessness, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consideration should be given to withdrawing tetra benzazine tablets treatment or initiating other symptomatic treatment (e.g., antidepressants) (see Adverse Reactions (6.1)).

Dosing Recommendation Above 50 mg per day
Patients who require doses of tetra benzazine tablets greater than 50 mg per day should be first tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme CYP2D6. The dose of tetra benzazine tablets should then be individualized accordingly to their status as PMs or EMs (see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

Extensive and Intermediate CYP2D6 Metabolizers
Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of tetra benzazine tablets above 50 mg per day should be titrated up slowly at weekly intervals by 12.5 mg daily, to allow the identification of a tolerated dose that reduces chorea. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended daily dose is 100 mg and the maximum recommended single dose is 37.5 mg. If adverse reactions such as alkalemia, parkinsonism, depression, insomnia, anxiety or sedation occur, titration should be stopped and the dose should be reduced. If the adverse reaction does not resolve, consideration should be given to withdrawing tetra benzazine tablets treatment or initiating other symptomatic treatment (e.g., antidepressants) (see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

Poor CYP2D6 Metabolizers
In PMs, the initial dose and titration is similar to EMs except that the recommended maximum single dose is 25 mg, and the recommended daily dose should not exceed a maximum of 50 mg (see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

Dose Adjustment with CYP2D6 Inhibitors
Strong CYP2D6 inhibitors
Medications that are strong CYP2D6 inhibitors such as quinidine or antidepressants (e.g., fluoxetine, paroxetine) significantly increase the exposure to $\pm$ -HTBZ and $\pm$ -HTBZ. Therefore, the total dose of tetra benzazine tablets should not exceed a maximum of 50 mg and the maximum single dose should not exceed 25 mg (see Warnings and Precautions (5.3), Drug Interactions (7.1), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

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

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

- DOSSAGE FORMS AND STRENGTHS**

Tetra benzazine tablets are available in the following strengths:

 - The 12.5 mg tetra benzazine tablets are white to off white, circular, flat faced beveled edge, non-scored, uncoated tablets debossed with 1 on one side.
 - The 25 mg tetra benzazine tablets are yellow, circular, flat faced beveled edge uncoated tablets debossed with 179 on one side and scored on the other.

- CONTRAINDICATIONS**

Tetra benzazine is contraindicated in patients:

 - Who are actively suicidal, or in patients with untreated or inadequately treated depression (see Warnings and Precautions (5.2)).
 - With hepatic impairment (see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)).
 - Taking monoamine oxidase inhibitors (MAOIs). Tetra benzazine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI (see Drug Interactions (7.3)).
 - Taking reserpine. At least 20 days should elapse after stopping reserpine before starting tetra benzazine (see Drug Interactions (7.2)).

- 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. In a 12-week controlled trial, tetra benzazine 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.

Prescribers should periodically re-evaluate the need for tetra benzazine in their patients by assessing the beneficial effect on chorea and possible adverse effects, including depression, cognitive decline, parkinsonism, dysphagia, sedation/somnolence, alkalemia, 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 tetra benzazine.

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

DOSSAGE FORMS AND STRENGTHS

Tablets: 12.5 mg non-scored and 25 mg scored (3)

CONTRAINDICATIONS

- Actively suicidal, or who have depression which is untreated or undertreated (4, 5.3)
- Hepatic impairment (4, 6, 12.3)
- Taking MAOIs or reserpine (4, 7.2, 7.3)

WARNINGS AND PRECAUTIONS

- Periodically reevaluate the benefit and potential for adverse effects such as worsening mood, cognition, rigidity, and functional capacity (5.1)
- Do not exceed 50 mg/day and the maximum single dose should not exceed 25 mg if administered in conjunction with a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine) (5.3, 7.1)
- Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs (5.4, 5.6)
- Restlessness, agitation, alkalemia and parkinsonism: Reduce dose or discontinue if occurs (5.5, 5.6)
- Dysphagia and aspiration pneumonia: Monitor for dysphagia (5.7)
- Sedation/Somnolence: May impair patient's ability to drive or operate complex machinery (5.8)
- OTc prolongation: Not recommended in combination with other drugs that prolong OTc (5.9)
- Exaggerated orthostatic hypotension: When used with drugs that reduce or antagonize dopamine. Discontinue tetra benzazine if this occurs (5.12)

ADVERSE REACTIONS

Most common adverse reactions (>10% and at least 5% greater than placebo) were: Sedation / somnolence, fatigue, insomnia, depression, alkalemia, anxiety, nausea (5.1)

Report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-816-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, tetra benzazine may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2015

- USE IN SPECIFIC POPULATIONS**

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

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 tetra benzazine were reported to have an adverse event of depression or worsening depression compared to none of the 50 placebo-treated patients in two open-label studies. In one study, 29 patients received tetra benzazine for up to 48 weeks; in the second study, 75 patients received tetra benzazine for up to 80 weeks). The rate of depression/worsening depression was 55%.

In all of the HD chorea studies of tetra benzazine (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 ranged from 3 to 13% and over 25% of patients attempt suicide at some point in their lives.

Patients, their caregivers, and families should be informed of the risk of depression, worsening depression, and suicidality associated with tetra benzazine and should be instructed to report behaviors of concern promptly to the treating physician. Patients should be advised that if their decision should be to discontinue tetra benzazine.

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

Patients who are PMs of tetra benzazine will have substantially higher levels of the primary drug metabolites (about 3-fold for $\pm$ -HTBZ and 9-fold for $\pm$ -HTBZ) than patients who are EMs. The dosage should be adjusted according to a patient's CYP2D6 metabolizer status. In patients who are identified as CYP2D6 PMs, the maximum recommended total daily dose is 50 mg and the maximum recommended single dose is 25 mg (see Dose and Administration (2.2), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

5.6 Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with tetra benzazine and other drugs that reduce dopamine's transmission (see Warnings and Precautions (5.2), Drug Interactions (7.6)). Clinical manifestations of NMS are hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria, rhabdomyolysis, and acute renal failure. The diagnosis of NMS can be complicated, other serious medical illness (e.g., pneumonia, systemic infection), and untreated or inadequately treated extrapyramidal disorders can present with similar signs and symptoms. Other important considerations in the differential diagnosis include central adrenergic toxicity, toxic stroke, drug fever, and primary central nervous system pathology.

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

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

5.5 Alkalemia, Restlessness, and Agitation
In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with HD, alkalemia was observed in 10 (19%) of tetra benzazine-treated patients and 0% of placebo-treated patients. In an 80-week open-label study, alkalemia was observed in 20% of tetra benzazine-treated patients. Alkalemia was not observed in a 48-week open-label study. Patients receiving tetra benzazine should be monitored for the presence of alkalemia. Patients receiving tetra benzazine should also be monitored for signs and symptoms of restlessness and agitation, as they may be indicators of developing alkalemia. If a patient develops alkalemia, the tetra benzazine dose should be reduced; however, some patients may require discontinuation of therapy.

5.8 Parkinsonism
Tetra benzazine can cause parkinsonism. In a 12-week double-blind, placebo-controlled study in patients with chorea associated with HD, symptoms suggestive of parkinsonism (i.e., bradykinesia, hypotonia and rigidity) were observed in 15% of tetra benzazine-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 tetra benzazine-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 tetra benzazine, dose reduction should be considered; in some patients, discontinuation of therapy may be necessary.

5.7 Dysphagia
Dysphagia is a component of HD. However, drugs that reduce dopaminergic transmission have been associated with esophageal dysmotility and dysphagia. Dysphagia may be associated with aspiration pneumonia. In a 12-week, double-blind, placebo-controlled study in patients with chorea associated with HD, dysphagia was observed in 4% of tetra benzazine-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 tetra benzazine-treated patients, respectively. Some of the cases of dysphagia were associated with aspiration pneumonia. Whether these events were related to treatment is unknown.

5.6 Sedation and Somnolence
Sedation is the most common dose-limiting adverse reaction of tetra benzazine. In a 12-week, double-blind, placebo-controlled trial in patients with chorea associated with HD, sedation/somnolence occurred in 17.5% (31%) tetra benzazine-treated patients and 1 (1%) placebo-treated patient. Sedation was the reason upward titration of tetra benzazine was stopped and/or the dose of tetra benzazine was decreased in 15.5% (29%) patients. In all but one case, decreasing the dose of tetra benzazine resulted in decreased sedation. In 48-week and 80-week open-label studies, sedation/somnolence occurred in 17% and 57% of tetra benzazine-treated patients, respectively. In some patients, sedation occurred at doses that were lower than recommended doses.

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

5.9 OTc Prolongation
Tetra benzazine causes a small increase (about 8 msec) in the corrected QTc (QTc) interval. OTc prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases (see Clinical Pharmacology (12.2)).

The use of tetra benzazine should be avoided in combination with other drugs that are known to prolong QTc, including antiarrhythmic medications (e.g., chloroquine, haloperidol, disopyramide), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval (see Drug Interactions (7.3)).

Tetra benzazine should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia, (2) hypokalemia or hypomagnesemia, (3) concomitant use of other drugs that prolong the QTc interval, and (4) presence of congenital prolongation of the QT interval (see Clinical Pharmacology (12.2)).

5.10 Hypotension and Orthostatic Hypotension
Tetra benzazine induced postural decreases 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 tetra benzazine-treated patients (vs. none in placebo) in the 12-week controlled trial; however, blood pressure was not measured during these events. Monitoring of vital signs on standing should be considered in patients who are vulnerable to hypotension.

5.11 Hyperreflexia/Insomnia
Tetra benzazine elevates serum prolactin concentrations in humans. Following administration of 25 mg to healthy volunteers, peak 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 tetra benzazine 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 tetra benzazine 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 tetra benzazine.

5.12 Tardive Dyskinesia (TD)
A potentially irreversible syndrome of involuntary, dyskinetic movements may develop in patients treated with neuroleptic drugs. In an animal model of tardive dyskinesia, acute administration of reserpine, a monoamine depletor, has been shown to produce excessive 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 tetra benzazine, which are dopamine depletors, have been reported to cause tardive dyskinesia in humans, but as pre-synaptic dopamine depletion could theoretically lead to supersensitivity to dopamine, and tetra benzazine can cause the extrapyramidal symptoms also known to be associated with neuroleptics (e.g., parkinsonism and alkalemia), physicians should be aware of the possible risk of tardive dyskinesia. If signs and symptoms of TD appear in a patient treated with tetra benzazine, drug discontinuation should be considered.

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

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

ADVERSE REACTIONS

The following serious adverse reactions are described below and in elsewhere in the labeling:

- Depression and suicidality (see Warnings and Precautions (5.2))
- Alkalemia, restlessness, and agitation (see Warnings and Precautions (5.5))
- Parkinsonism (see Warnings and Precautions (5.8))
- Dysphagia (see Warnings and Precautions (5.7))
- Sedation and somnolence (see Warnings and Precautions (5.6))

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

In a randomized, 12-week, placebo-controlled clinical trial of HD patients, adverse reactions were more common in the tetra benzazine group than in the placebo group. For 10% of 54 (91%) patients who received tetra benzazine experienced one or more adverse reactions at any time during the study. The most common adverse reactions were (over 10%, and at least 5% greater than placebo) were sedation/somnolence, fatigue, insomnia, depression, alkalemia, and nausea.

Adverse Reactions Occurring in $\geq 4\%$ Patients
The number and percentage of the most common adverse reactions that occurred at any time during the study in $> 4\%$ of tetra benzazine-treated patients, and with greater frequency than placebo-treated patients, are presented in Table 1.

Table 1: Adverse Reactions in a 12-Week, Double-Blind, Placebo-Controlled Trial in Patients with Huntington's Disease

Adverse Reaction	Tetra benzazine n = 54	Placebo n = 30
Sedation/somnolence	31	3
Insomnia	22	0
Depression	19	0
Anxiety/worsening depression	15	3
Irritability	9	0
Decreased appetite	4	0
Alkalemia	19	0
Balance difficulty	9	0
Parkinsonism/bradykinesia	4	0
Dizziness	4	0
Dysarthria	4	0
Unsteady gait	4	0
Nausea	13	7
Vomiting	6	3
Fatigue	22	13
Laceration (head)	6	0
Echymosis	6	0
Upper respiratory tract infection	11	7
Shortness of breath	4	0
Bronchitis	4	0
Dysuria	4	0

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

Adverse Reactions Due to Extrapyramidal Symptoms
Table 2 describes the incidence of events considered to be extrapyramidal adverse reactions which occurred at a greater frequency in tetra benzazine-treated patients compared to placebo-treated patients.

Table 2: Adverse Reactions Due to Extrapyramidal Symptoms in a 12-Week, Double-Blind, Placebo-Controlled Trial in Patients with Huntington's Disease

Adverse Reaction	Tetra benzazine n = 54	Placebo n = 30
Alkalemia ¹	19%	0
Extrapyramidal event ²	15%	0
Any extrapyramidal event	33%	0

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

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

Patients may have had events in more than one category.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of tetra benzazine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system disorders: tremor
Psychiatric disorders: confusion, worsening aggression
Respiratory disorders: respiratory distress, pneumonia
Skin and subcutaneous tissue disorders: hyperreflexia, skin rash

DRUG INTERACTIONS

7.1 Strong CYP2D6 Inhibitors
Because $\pm$ -HTBZ and $\pm$ -HTBZ are substrates for CYP2D6. Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, mephenytoin) increase exposure to these metabolites. A reduction in tetra benzazine dose may be necessary when adding a strong CYP2D6 inhibitor (e.g., paroxetine, fluoxetine) in patients maintained on a stable dose of tetra benzazine. The daily dose of tetra benzazine should not exceed 50 mg per day and the maximum single dose of tetra benzazine should not exceed 25 mg in patients taking strong CYP2D6 inhibitors (see Dose and Administration (2.2), Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

7.2 Reserpine
Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Prescribers should wait for chorea to reemerge before administering tetra benzazine to avoid overexposure and major depletion of serotonin and norepinephrine in the CNS. At least 20 days should elapse after stopping reserpine before starting tetra benzazine. Tetra benzazine and reserpine should not be used concomitantly (see Contraindications (4), Warnings and Precautions (5.2)).

7.3 Monoamine Oxidase Inhibitors (MAOIs)
Tetra benzazine is contraindicated in patients taking MAOIs. Tetra benzazine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI (see Contraindications (4), Warnings and Precautions (5.2)).

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

7.5 Drugs that Cause QTc Prolongation
Tetra benzazine causes a small prolongation of QTc (about 8 msec), concomitant use with other drugs that are known to cause QTc prolongation should be avoided, these including antiarrhythmic medications (e.g., chloroquine, haloperidol, disopyramide, 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. Tetra benzazine should be avoided in patients with congenital long QT syndrome, and in patients with a history of cardiac arrhythmia. Certain conditions may increase the risk for torsade de pointes or sudden death such as: (1) bradycardia, (2) hypokalemia or hypomagnesemia, (3) concomitant use of other drugs that prolong the QTc interval, and (4) presence of congenital prolongation of the QT interval (see Warnings and Precautions (5.3), Clinical Pharmacology (12.2)).

7.6 Neuroleptic Drugs
The risk for Parkinsonism, NMS, and alkalemia may be increased by concomitant use of tetra benzazine and dopamine antagonists or anticholinergics (e.g., chlorpromazine,

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

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

Impairment of Fertility

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

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

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

14 CLINICAL STUDIES

Study 1

The efficacy of tetrabenazine as a treatment for the chorea of Huntington's disease was established primarily in a randomized, double-blind, placebo-controlled multi-center trial (Study 1) conducted in ambulatory patients with a diagnosis of HD. The diagnosis of HD was based on family history, neurological exam, and genetic testing. Treatment duration was 12 weeks, including a 7-week dose titration period and a 5-week maintenance period followed by a 1-week washout. Tetrabenazine was started at a dose of 12.5 mg per day, followed by upward titration at weekly intervals, in 12.5 mg increments until satisfactory control of chorea was achieved. 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 patients in the drug group declined by an estimated 5 units during maintenance therapy (average of Week 9 and Week 12 scores versus baseline), compared to an estimated 1.5 units in the placebo group. The treatment effect of 3.5 units was statistically significant. At the Week 15 follow-up in Study 1 (11 weeks after discontinuation of the study medication), the Total Chorea Scores of patients receiving tetrabenazine returned to baseline.

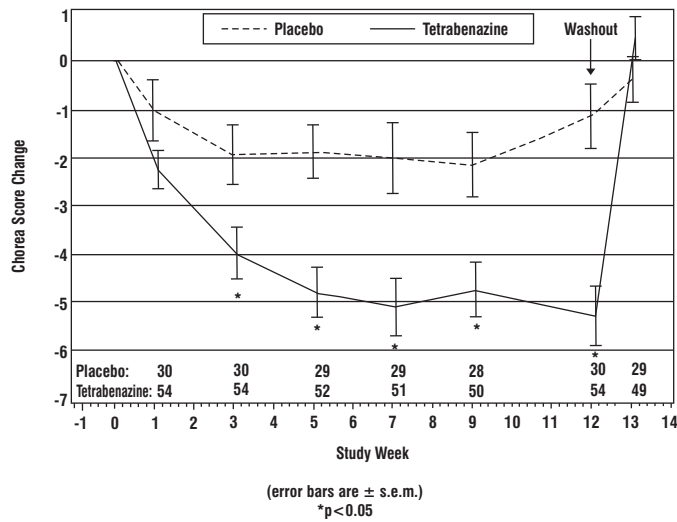


Figure 1. Mean $\pm$ s.e.m. Changes from Baseline in Total Chorea Score in 84 HD Patients Treated with Tetrabenazine (n=54) or Placebo (n=30)

Figure 2 illustrates the cumulative percentages of patients from the tetrabenazine and placebo treatment groups who achieved the level of reduction in the Total Chorea Score shown on the X-axis. The leftward shift of the curve (toward greater improvement) for the tetrabenazine-treated patients indicates that these patients were more likely to have any given degree of improvement in chorea score. 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 at Week 12 are shown in the insert table.

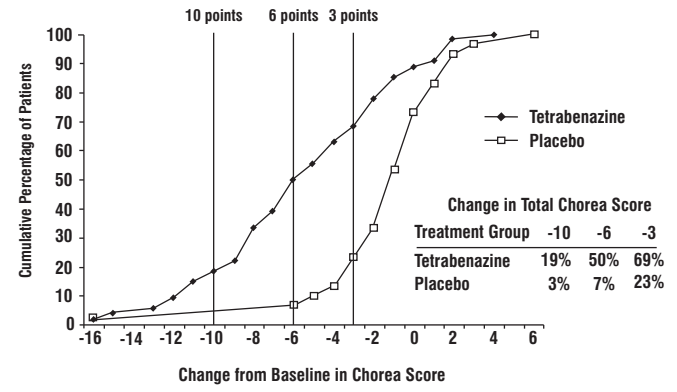


Figure 2. Cumulative Percentage of Patients with Specified Changes from Baseline in Total Chorea Score. The Percentages of Randomized Patients within each treatment group who completed Study 1 were: Placebo 97%, Tetrabenazine 1%.

A Physician-rated Clinical Global Impression (CGI) favored tetrabenazine statistically. In general, measures of functional capacity and cognition showed no difference between tetrabenazine 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 normally, a 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 tetrabenazine 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 tetrabenazine 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 2.5 units).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Tetrabenazine tablets are available in the following strengths and packages:

The 12.5 mg tetrabenazine tablets are white to off white, circular, flat faced beveled edge, non-scored, uncoated tablets debossed with T on one side.

Bottles of 112's with Child Resistant Cap.....NDC 47335-277-23

The 25 mg tetrabenazine tablets are yellow, circular, flat faced beveled edge uncoated tablets debossed with 179 on one side and scored on other side.

Bottles of 112's with Child Resistant Cap.....NDC 47335-179-23

16.2 Storage

Store tetrabenazine tablets at 20° to 25°C (68° to 77°F), excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Suicidality

Inform patients and their families that tetrabenazine may increase the risk of suicidal thinking and behaviors. Counsel patients and their families to remain alert to the emergence of suicidal ideation and to report it immediately to the patient's physician [see Contraindications (4), Warnings and Precautions (5.2)].

Risk of Depression

Inform patients and their families that tetrabenazine may cause depression or may worsen pre-existing depression. Encourage patients and their families to be alert to the emergence of sadness, worsening of depression, withdrawal, insomnia, irritability, hostility (aggressiveness), anhedonia (loss of interest in activities), anxiety, agitation, or panic attacks and to report such symptoms promptly to the patient's physician [see Contraindications (4), Warnings and Precautions (5.2)].

Dosing of Tetrabenazine

Inform patients and their families that the dose of tetrabenazine will be increased slowly to the dose that is best for each patient. Sedation, akathisia, parkinsonism, depression, and difficulty swallowing may occur. Such symptoms should be promptly reported to the physician and the tetrabenazine may dose need to be reduced or discontinued [see Dosage and Administration (2.2)].

Risk of Sedation and Somnolence

Inform patients that tetrabenazine may induce sedation and somnolence and may impair the ability to perform tasks that require complex motor and mental skills. Advise patients that until they learn how they respond to tetrabenazine, they should be careful doing activities that require them to be alert, such as driving a car or operating machinery [see Warnings and Precautions (5.8)].

Interaction with Alcohol

Advise patients and their families that alcohol may potentiate the sedation induced by tetrabenazine [see Drug Interactions (7.4)].

Usage in Pregnancy

Advise patients and their families to notify the physician if the patient becomes pregnant or intends to become pregnant during tetrabenazine therapy, or is breast-feeding or intending to breast-feed an infant during therapy [see Use in Specific Populations (8.1)].

MEDICATION GUIDE

Tetrabenazine Tablets
(TET-ra-BEN-a-zine)

Read the Medication Guide that comes with tetrabenazine tablets 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 tetrabenazine tablets?

- Tetrabenazine tablets can cause serious side effects, including:**
 - depression
 - suicidal thoughts
 - suicidal actions
- You should not start taking tetrabenazine tablets 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 tetrabenazine tablets are 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:

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

What are tetrabenazine tablets?

Tetrabenazine tablets are medicines that are used to treat the involuntary movements (chorea) of Huntington's disease. Tetrabenazine tablets do 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 tetrabenazine tablets are safe and effective in children.

Who should not take tetrabenazine tablets?

Do not take tetrabenazine tablets if you:

- are depressed or have thoughts of suicide. See "What is the most important information I should know about tetrabenazine tablets?"
- 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 Serpax[®] and Renese[®]-R) with tetrabenazine tablets. If your doctor plans to switch you from taking reserpine to tetrabenazine tablets, you must wait at least 20 days after your last dose of reserpine before you start taking tetrabenazine tablets.**

What should I tell my doctor before taking tetrabenazine tablets?

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 tetrabenazine tablets.
- 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 tetrabenazine tablets can harm your unborn baby.
- are breast-feeding. It is not known if tetrabenazine passes into breast milk.

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

How should I take tetrabenazine tablets?

- Tetrabenazine tablet is a tablet that you take by mouth.
- Take tetrabenazine tablets exactly as prescribed by your doctor.**
- You must take tetrabenazine tablets with or without food.
- Your doctor will increase your dose of tetrabenazine tablets each week for several weeks, until you and your doctor find the best dose for you.
- If you stop taking tetrabenazine tablets or miss a dose, your involuntary movements may return or worsen in 12 to 18 hours after the last dose.
- Before starting tetrabenazine tablets, you should talk to your healthcare provider about what to do if you miss a dose. If you miss a dose and it is time for your next dose, do not double the dose.
- Tell your doctor if you stop taking tetrabenazine tablets 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 tetrabenazine tablets each day, you will need to have a blood test to see if it is safe for you.**

What should I avoid while taking tetrabenazine tablets?

Sleepiness (sedation) is a common side effect of tetrabenazine tablets. While taking tetrabenazine tablets, **do not drive a car or operate dangerous machinery until you know how tetrabenazine tablets affect you.** Drinking alcohol and taking other drugs that may also cause sleepiness while you are taking tetrabenazine tablets may increase any sleepiness caused by tetrabenazine tablets.

What are the possible side effects of tetrabenazine tablets?

Tetrabenazine tablets can cause serious side effects, including:

- Depression, suicidal thoughts, or actions.** See "What is the most important information I should know about tetrabenazine tablets?"
- 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.** Tetrabenazine tablets 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.** Tetrabenazine tablets increase your chance of having certain changes in the electrical activity in your heart which can be seen on an electrocardiogram (ECG). These changes can lead to a dangerous abnormal heartbeat. Taking tetrabenazine tablets with certain medicines may increase this chance.
- Difficulties 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 tetrabenazine tablets. Tell your doctor right away if you get dizzy or feel weak when taking tetrabenazine tablets. Your doctor may need to watch your blood pressure closely.
- Tongue 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. Tetrabenazine tablets work like other drugs that can cause TD. If you get TD with tetrabenazine tablets, it is possible that the TD will not go away.

Common side effects with tetrabenazine tablets 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 tetrabenazine tablets 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 tetrabenazine tablets

Tetrabenazine tablets contain the active ingredient tetrabenazine. It also contains these inactive ingredients: anhydrous lactose, corn starch, sodium starch glycolate Type A potato, ferric oxide yellow (for 25 mg), colloidal silicon dioxide, magnesium stearate and talc.

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

This Medication Guide summarizes the most important information about tetrabenazine tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about tetrabenazine tablets that's written for healthcare professionals. You can also call 1-800-818-4555.

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

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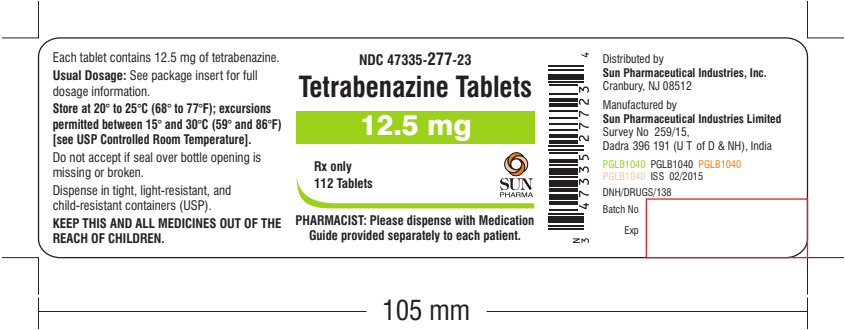
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570--14 Zigzag--40 mm

430 mm

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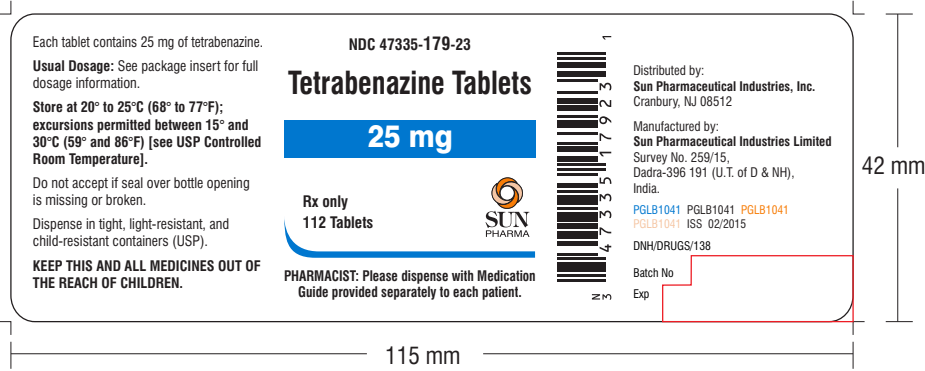


Size: 105x30 mm

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Unvarnish area: 22 x 8 mm

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Size: 115x42mm

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