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Terabazine Tablets  
12.5 mg and 25 mg

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### TETRABAZINE 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 (5.2)**
- **Balance risks of depression and suicidality with the clinical need for control of chorea when considering the use of terabazine 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 (5.2)**
- **Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.2)**
- **Terabazine tablets are contraindicated in patients who are actively suicidal, and in patients with untreated or inadequately treated depression (4.5.2)**

### INDICATIONS AND USAGE

Terabazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease (1)

### DOSE AND ADMINISTRATION

- Initiation of dose with careful weekly titration is required. The 1<sup>st</sup> week's starting dose is 12.5 mg daily; 2<sup>nd</sup> week, 25 mg (12.5 mg twice daily); thereafter slowly titrate at weekly intervals by 12.5 mg to a tolerated dose that reduces chorea (2.1, 2.2)
- Doses of 37.5 mg and up to 50 mg per day should be administered in three divided doses per day with 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, 5.3)
- Maximum daily dose in PMs: 50 mg with a maximum single dose of 25 mg (2.2)
- Maximum daily dose in EMs and intermediate metabolizers (IMs): 100 mg with a maximum single dose of 25 mg (2.2)
- If serious adverse reactions occur, terabazine should be stopped and the dose should be reduced. If adverse reactions do not resolve, consider withdrawal of terabazine tablets (2.2)

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### FULL PRESCRIBING INFORMATION

#### WARNING: DEPRESSION AND SUICIDALITY

Terabazine tablets can increase the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease. Anyone considering the use of terabazine 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 (5.2).

Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, who are actively suicidal, and in patients with untreated or inadequately treated depression (see Contraindications (4), Warnings and Precautions (5.2)).

#### 1 INDICATIONS AND USAGE

Terabazine is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease.

#### 2 DOSE AND ADMINISTRATION

**2.1 General Dosing Considerations**  
The chronic daily dose of terabazine tablets used to treat chorea associated with Huntington's disease (HD) is determined individually for each patient. When first prescribed, terabazine tablet therapy should be titrated slowly over several weeks to identify a dose of terabazine tablets that reduces chorea and is tolerated. Terabazine tablets can be administered without regard to food (see Dosage Administration (2.3)).

#### 2.2 Individualization of Dose

Dosing Recommendations Up to 50 mg per day  
The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given 12.5 mg twice a day. Terabazine 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. Doses above 50 mg per day should be given in a three times a day regimen. The maximum recommended single dose is 25 mg. If adverse reactions such as akathisia, 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 terabazine tablets treatment or initiating other specific treatment (e.g., antidepressants) (see Warnings and Precautions (5.1), (5.2), Drug Interactions (7.1)).

#### Dosing Recommendations Above 50 mg per day

Patients who require doses of terabazine 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 terabazine tablets should not exceed 25 mg (see Warnings and Precautions (5.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)).

**Extensive or Intermediate CYP2D6 Metabolizers**  
Genotyped patients who are identified as extensive (EMs) or intermediate metabolizers (IMs) of CYP2D6, who need doses of terabazine 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 25 mg. If adverse reactions such as akathisia, 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 terabazine tablets treatment or initiating other specific 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)).

#### 2.3 Dosage 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 *o*-HTZ and *p*-HTZ. Therefore, the total dose of terabazine 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)).

#### 2.4 Discontinuation of Treatment

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

#### 2.5 Resumption of Treatment

Following treatment interruption of greater than five (5) days, terabazine 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.

#### 3 DOSAGE FORMS AND STRENGTHS

Terabazine tablets are available in the following strengths:

- The 12.5 mg terabazine tablets are white to off-white, circular, flat faced beveled edge, non-scored, uncoated tablets debossed with "10n side".
- The 25 mg terabazine tablets are yellow, circular, flat faced beveled edge uncoated tablets debossed with "10n" on one side and scored on other side.

#### 4 CONTRAINDICATIONS

Terabazine 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). Terabazine 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 terabazine (see Drug Interactions (7.2)).

#### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Clinical Warnings 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, terabazine was shown to cause slight worsening in mood, cognition, rigidity, and functional capacity. Whether these effects represent, resolve, or worsen with continued treatment is unknown.

Prescribers should periodically evaluate the need for terabazine in their patients by assessing the beneficial effect of chorea and possible adverse effects, including depression, cognitive decline, parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness and disability. It may be difficult to distinguish between drug-induced side-effects and progression of the underlying disease, decreasing the dose or stopping the drug may help the clinician distinguish between the two possibilities. In some patients, underlying chorea itself may improve over time, decreasing the need for terabazine.

#### 5.2 Depression and Suicidality

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

#### DOSE 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 under treated (4.5.3)
- Hepatic impairment (4.5.1, 4.5.2)
- Taking MAOIs or reserpine (4.7.2, 7.3)

#### WARNINGS AND PRECAUTIONS

- Periodically evaluate 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, 7.6)
- Restlessness, agitation, akathisia and parkinsonism: Reduced dose or discontinuation (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)
- QTc prolongation: Not recommended in combination with other drugs that prolong QTc (5.9)
- Exaggerated extrapyramidal disorders when used with other drugs that reduce or antagonize dopamine: Discontinue terabazine 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, akathisia, anxiety, nausea (8.1).

To report suspected adverse reactions, contact Sun Pharmaceutical Industries, Inc. at 1-800-811-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

#### USE IN SPECIFIC POPULATIONS

Preparation Based on Animal Data, terabazine may cause fetal harm (8.1)

#### See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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

**5.12 Tardive Dyskinesia (TD)**  
A potentially reversible 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 terabazine, which are dopamine depletors, have been reported to cause clear tardive dyskinesia in humans, but an pre-synaptic dopamine depletion could theoretically lead to supersensitivity to dopamine, and terabazine 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 terabazine, drug discontinuation should be considered.

**5.13 Binding to Melanin-Containing Tissues**  
Since terabazine or its metabolites bind to melanin-containing tissues, it could accumulate in these tissues over time. This raises the possibility that terabazine 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 treatment.

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

#### 6 ADVERSE REACTIONS

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

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

**6.1 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 rates observed in practice.

During the development, terabazine was administered to 773 unique subjects and patients. The conditions and duration of exposure to terabazine varied greatly, and detailed single and multiple dose clinical pharmacology studies in healthy volunteers (N=259) and open-label (N=529) 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 terabazine group than in the placebo group. Forty-one of 54 (81%) patients who received terabazine experienced one or more adverse reactions at any time during the study. The most common adverse reactions were fatigue (10%), and at least 5% greater than placebo) were sedation/somnolence, fatigue, insomnia, depression, akathisia, and nausea.

Adverse Reactions Occurring in >4% Patients  
The number and percentage of the most common adverse reactions that occurred at any time during the study in > 4% of terabazine-treated patients, and with a greater frequency than in 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	Terabazine n = 54	Placebo n = 30
Sedation/somnolence	21	0
Insomnia	22	0
Depression	19	0
Anxiety/agitation	15	3
irritability	9	3
Decreased appetite	4	0
Obsessive reaction	4	0
Akathisia	19	0
Balance difficulty	9	0
Parkinsonism/bra/dykesia	9	0
Dizziness	4	0
Dysphagia	4	0
Unstable gait	4	0
Headache	4	3
Nausea	13	7
Yawning	6	3
Fatigue	22	13
Fall	15	13
Laceration (hand)	22	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 (51%) patients randomized to terabazine. These adverse reactions consisted of sedation (15), akathisia (7), parkinsonism (4), depression (3), anxiety (2), fatigue (1), and dizziness (1). Some patients had more than one AE and, therefore, counted more than once.

**Adverse Reactions Due to Extrapyramidal Symptoms**  
Table 2 summarizes the incidence of events considered to be extrapyramidal adverse reactions which occurred at a greater frequency in terabazine-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**

Terabazine n = 54	Placebo n = 30	
Akathisia <sup>1</sup>	19%	0
Extrapyramidal event <sup>1</sup>	15%	0
Any extrapyramidal event	33%	0

<sup>1</sup> Patients with the following adverse event preferred terms were counted in this category: akathisia, hyperkinesia, restlessness. Patients with the following adverse event preferred terms were counted in this category: bradykinesia, parkinsonism, extrapyramidal disorder, hypernesia.

Patients may have had events in more than one category.

**6.2 Postmarketing Experience**  
The 2 categories of adverse events were not identified during post-approval use of terabazine. 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 use.

Nervous system disorders, tremor  
Psychiatric disorders, worsening aggression  
Respiratory, thoracic and mediastinal disorders, pneumonia  
Skin and subcutaneous tissue disorders, hyperhidrosis, skin rash

#### 7 DRUG INTERACTIONS

**7.1 Strong CYP2D6 Inhibitors**  
In vitro studies indicate that *o*-HTZ and *p*-HTZ are substrates for CYP2D6. Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) markedly increase exposure to these metabolites. A reduction in terabazine dose may be necessary when adding a strong CYP2D6 inhibitor to patients maintained on a stable dose of terabazine. The daily dose of terabazine should not exceed 50 mg per day and the maximum single dose of terabazine should not exceed 25 mg in patients taking strong CYP2D6 inhibitors (see Dosage and Administration (2.3), Warnings and Precautions (5.3), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)).

**7.2 Reserpine**  
Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Prescribers should wait for chorea to reemerge before administering terabazine to avoid overexposure and major depletion of serotonin and norepinephrine in the CNS. At least 20 days should elapse after stopping reserpine before starting terabazine. Terabazine and reserpine should not be used concomitantly (see Contraindications (4), Warnings and Precautions (5.12)).

**7.3 Monoamine Oxidase Inhibitors (MAOIs)**  
Terabazine is contraindicated in patients taking an MAOI (see Contraindications (4), Warnings and Precautions (5.12)).

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

**7.5 Drugs that Cause QTc Prolongation**  
Terabazine 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 include antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class IA (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or other medications known to prolong the QTc interval. Terabazine should not be used in patients with congenital long QT syndrome, and in patients with a history of cardiac arrhythmias. 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 Clinical Pharmacology (12.2)).

**7.6 Neuroleptic Drugs**  
The risk for Parkinsonism, NMS, and akathisia may be increased by concomitant use of terabazine and dopamine antagonists or antipsychotics (e.g., chlorpromazine, haloperidol, clozapine, risperidone, thioridazine, ziprasidone).

#### 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy**  
Pregnancy Category C  
There are no adequate and well-controlled studies in pregnant women. Terabazine should be used during pregnancy only if the potential benefits justifies the potential risks to the fetus.

Terabazine had no clear effects on embryonic/fetal development when administered to pregnant rats during 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<sup>2</sup> basis). Terabazine had no effects on embryonic/fetal development when administered to pregnant rabbits during the period of organogenesis at oral doses up to 60 mg/kg/day (12 times the MRHD on a mg/m<sup>2</sup> basis). Because neither rat nor rabbit doses with terabazine produce 9-desmethyl-beta-DHTZ, a major human metabolite, these studies may not have adequately addressed the potential effects of terabazine on embryonic/fetal development in humans.

When terabazine 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 in 15 and 30 mg/kg/day and delayed pup maturation was observed at all doses. The most effect for stillbirths and postnatal mortality was 0.5 times the MRHD on a mg/m<sup>2</sup> basis. Because rats dosed with terabazine do not produce 9-desmethyl-beta-DHTZ, a major human metabolite, this study may not have adequately assessed the potential effects of terabazine on the offspring of women exposed in utero and in lactation.

**8.2 Labor and Delivery**  
The effect of terabazine on labor and delivery in humans is unknown.

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

**8.4 Pediatric Use**  
The safety and efficacy of terabazine in pediatric patients have not been established.

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

**8.6 Hepatic Impairment**  
Because the safety and efficacy of the increased exposure to terabazine and other circulating metabolites are unknown, it is not possible to adjust the dosage of terabazine in hepatic impairment to ensure safe use. The use of terabazine in patients with hepatic impairment is contraindicated (see Contraindications (4), Clinical Pharmacology (12.3)).

**8.7 Poor or Extensive CYP2D6 Metabolizers**  
Patients who require doses of terabazine greater than 50 mg per day should be first tested and genotyped to determine if they are poor (PM) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6. The dose of terabazine should then be individualized according to their status as either poor (PMs) or extensive metabolizers (EMs) (see Dosage and Administration (2.3), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)).

**Poor Metabolizers**  
Poor CYP2D6 metabolizers (PMs) will have substantially higher levels of exposure to the primary metabolites (about 3-fold for *o*-HTZ and 9-fold for *p*-HTZ) compared to EMs. The dosage should therefore, be adjusted according to a patient's CYP2D6 metabolizer status by limiting a single dose to a maximum of 25 mg and the recommended daily dose not to exceed a maximum of 50 mg/day in patients who are CYP2D6 PMs (see Dosage and Administration (2.3), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)).

**Extensive or Intermediate Metabolizers**  
In extensive (EMs) or intermediate metabolizers (IMs), the dosage of terabazine can be titrated to a maximum single dose of 25 mg and a recommended maximum daily dose of 100 mg (see Dosage and Administration (2.3), Drug Interactions (7.1), Clinical Pharmacology (12.3)).

#### 9 DRUG ABUSE AND DEPENDENCE

**9.1 Controlled Substance**  
Terabazine is not a controlled substance.

**9.2 Abuse**  
Clinical trials did not reveal patterns of drug seeking behavior, though these observations were not systematic. Abuse has not been reported from the postmarketing experience in countries where terabazine has been marketed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No increase in tumors was observed in p53<sup>-/-</sup> 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 8-dehydroxy-beta-DHTZ, 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  $\alpha$ -HTZ and  $\beta$ -HTZ 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.  $\alpha$ -HTZ and  $\beta$ -HTZ 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-DHTZ, 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 MRPD on a mg/m<sup>2</sup> 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 MRPD on a mg/m<sup>2</sup> basis) prior to and throughout mating with untreated females.

Because rats dosed with tetrabenazine do not produce 9-desmethyl-beta-DHTZ, 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 scores range 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 13 follow-up in Study 1 (1 week after discontinuation of the study medication), the Total Chorea Scores of patients receiving tetrabenazine returned to baseline.

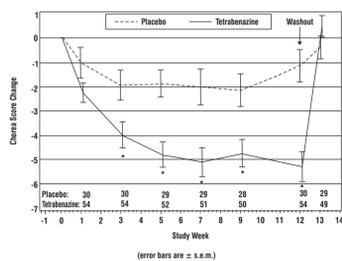


Figure 1. Mean ± s.e.m. Changes from Baseline in Total Chorea Score in 84 HD Patients Treated with Tetrabenazine (n=54) or Placebo (n=30)

Figure 2 illustrates the cumulative percentage 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 to Week 12 are shown in the inset table.

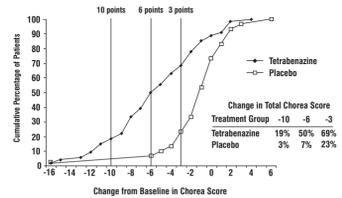


Figure 2. Cumulative Percentage of Patients with Specified Changes from Baseline in Total Chorea Score. The Percentage of Randomized Patients within each treatment group who completed Study 1 were: Placebo 97%, Tetrabenazine 91%.

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 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 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 3.5 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 "1" 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), suicidal (psychomotor) restlessness, 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, ataxia, 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) and 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 unimportant
- 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 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 risperidone. Do not take medicines that contain risperidone (such as *Seripenol*<sup>®</sup> and *Resperal*<sup>®</sup>) with tetrabenazine tablets. If your doctor plans to switch you from taking risperidone to tetrabenazine tablets, you must wait at least 20 days after your last dose of risperidone 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 may 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 miss a dose of 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.
  - Dizziness due to blood pressure changes when you change position (orthostatic hypotension). Change positions slowly from lying down to sitting up and from sitting up to standing when taking tetrabenazine tablets. Tell your doctor right away if you get dizzy or faint while taking tetrabenazine tablets. Your doctor may need to watch your blood pressure closely.
  - Tardive dyskinesia (TD). TD is a condition where there is repeated facial grimacing that cannot be controlled, sticking out of the tongue, smacking of the lips, puckering and pursing of the lips, and rapid eye blinking. 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
- irritability
- 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, polyd, 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 is 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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Folding  
430-4 Zigzag--40 mm  
570-14 Zigzag--40 mm

430 mm

Size: 430x570 mm

Each tablet contains 12.5 mg of tetrabenazine.

**Usual Dosage:** See package insert for full dosage information.

**Store 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].**

Do not accept if seal over bottle opening is missing or broken.

Dispense in tight, light-resistant, and child-resistant containers (USP).

**KEEP THIS AND ALL MEDICINES OUT OF THE REACH OF CHILDREN.**

NDC 47335-277-23

**Tetrabenazine Tablets**

**12.5 mg**

Rx only  
112 Tablets

PHARMACIST: Please dispense with Medication Guide provided separately to each patient.

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PGLB1040 PGLB1040 PGLB1040  
PGLB1040 ISS 02/2015  
DNH/DRUGS/138

Batch No  
Exp

105 mm

Size: 105x30 mm

[CRC]

Unvarnish area: 22 x 8 mm



(b) (4)

Each tablet contains 25 mg of tetrabenazine.

**Usual Dosage:** See package insert for full dosage information.

**Store 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].**

Do not accept if seal over bottle opening is missing or broken.

Dispense in tight, light-resistant, and child-resistant containers (USP).

**KEEP THIS AND ALL MEDICINES OUT OF THE REACH OF CHILDREN.**

NDC 47335-179-23

**Tetrabenazine Tablets**

**25 mg**

Rx only  
112 Tablets



PHARMACIST: Please dispense with Medication Guide provided separately to each patient.

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India.

PGLB1041 PGLB1041 PGLB1041  
PGLB1041 ISS: 02/2015

DNH/DRUGS/138

Batch No [redacted]  
Exp [redacted]

47335179231

42 mm

115 mm

Size: 115x42mm

[CRC]

[redacted] Unvarnish area: 26 x 9 mm



(b) (4)

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95  
75  
25  
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