### VMAT-2 Inhibitors: Deutetrabenazine, Tetrabenazine and Valbenazine Criterias for Use for the Treatment of Tardive Dyskinesia
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at the [PBM INTERnet](https://www.cmopnational.va.gov/cmop/PBM/Special%20Handling%20Drugs/forms/AllItems.aspx) or [PBM INTRAnet](https://vaww.cmopnational.va.gov/cmop/PBM/Special%20Handling%20Drugs/forms/AllItems.aspx) site for further information.

Valbenazine is subject to special handling drug procurement programs:

https://vaww.cmopnational.va.gov/cmop/PBM/Special%20Handling%20Drugs/forms/AllItems.aspx

Separate Criteria for Use are available for VMAT2 inhibitors for the treatment of Huntington’s disease and dystonia.

### Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive a VMAT2 inhibitor.

**FOR ALL VMAT2 INHIBITORS:**

- Patients is actively suicidal or with untreated or inadequately treated depression.
- Congenital long QT interval, or a QTc >450 ms for men or QTc >470 ms for women.
- History of cardiac arrhythmias (patients with a history of ventricular arrhythmias), cardiac conduction system disease (LBBB or RBBB) or cardiac device can be considered candidates with cardiology evaluation.
- Concurrent use of a monoamine oxidase inhibitor (MAOI).
- Current or use of reserpine within the past 20 days.
- Concurrent use of another VMAT2 inhibitor.
- A history of neuroleptic malignant syndrome (NMS).
- Current clinically significant hyperprolactinemia.
- Pregnant or breast feeding.

**Deutetrabenazine only**

- Hepatic impairment.

**Tetrabenazine only**

- Hepatic impairment.
- Patient is receiving a medication known to increase the QTc interval, e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone, antibiotics (e.g., moxifloxacin), Class IA (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval.

Updated version may be found at [PBM INTERnet](https://www.cmopnational.va.gov/cmop/PBM/Special%20Handling%20Drugs/forms/AllItems.aspx) or [PBM INTRAnet](https://vaww.cmopnational.va.gov/cmop/PBM/Special%20Handling%20Drugs/forms/AllItems.aspx)
Valbenazine only

- Creatinine clearance (CrCl) < 30 mL/min.
- Concurrent use of a strong CYP3A4 inducer.

Inclusion Criteria

The answers to all of the following must be fulfilled in order to meet criteria.

- The patient has a diagnosis of tardive dyskinesia (TD) secondary to a dopaminergic blocking agent, e.g. antipsychotic or metoclopramide.
- The patient’s TD interferes with the patient’s functional status, including self-care and ambulation; quality of life; or creates a social stigma sufficient to cause social isolation or embarrassment.
- The prescriber has documented the specific movement(s) (e.g., facial, oral extremity, or trunk) in the patient’s medical record along with how TD is affecting the patient’s function, quality of life or socialization.
- A recent Abnormal Involuntary Movement Scale (AIMS) score is recorded in the patient’s medical record.
- An ECG was performed to confirm a QTc < 450 ms for men or QTc < 470 ms for women.
- When the initial prescriber is a resident, fellow or other trainee, an attending psychiatrist or neurologist has verified the diagnosis and need for a VMAT2 inhibitor.

Renewal Criteria

- When the initial prescriber is a resident, fellow or other trainee, an attending psychiatrist or neurologist has verified the benefit and continued need for a VMAT2 inhibitor.

  After 12 weeks:
  - Improvement in the specific movement(s) is documented in the patient’s medical record along with how it has positively affected the patient’s function, quality of life or socialization.
  - An AIMS score is documented in the patient’s medical record.

  Every 6 months thereafter:
  - A sustained or continued improvement in the specific movement(s) or dystonia is documented in the patient’s medical record along with how it has positively affected the patient’s function, quality of life or socialization.
  - An AIMS score is documented in the patient’s medical record.

Dosage and Administration

Deutetrabenazine

- Deutetrabenazine is to be taken whole with food. Tablets should not be crushed, chewed or broken.
- The starting dose is 6 mg taken two times a day (12 mg/day). After one week the dose of deutetrabenazine may be increased by 6 mg weekly until Week 7 to a dose of 24 mg two times a day (48 mg/day).
- In patients who are poor CYP2D6 metabolizers, or who are receiving strong CYP2D6 inhibitors.
VMAT2 Inhibitors: Deutetrabenazine, Tetrabenazine, and Valbenazine

(e.g., quinidine, paroxetine, fluoxetine, and bupropion), the total daily dosage of deutetrabenazine should not exceed 36 mg (18 mg twice daily).

- For patients requiring deutetrabenazine doses greater than 24 mg per day, who are using deutetrabenazine with other drugs known to prolong QTc, assess the QTc interval before and after increasing the dose of deutetrabenazine or the other drugs.
- Patients should be assessed and monitored closely for clinical worsening, suicidality, or unusual changes in behavior.

Tetrabenazine
- Tetrabenazine can be taken without regard to meals.
- The starting dose should be 12.5 mg per day given once in the morning. After one week, the dose should be increased to 25 mg per day given as 12.5 mg twice a day. Tetrabenazine should be titrated up slowly at weekly intervals by 12.5 mg, to allow the identification of a dose that reduces chorea and is well tolerated. If a total daily dose (TDD) of 37.5 mg or more is needed, it should be given in divided doses three times a day. The maximum recommended single dose is 25 mg for a patient taking a TDD of less than or equal to 50 mg.
- The manufacturer recommends CYP2D6 genotyping for doses greater than 50 mg daily.
- Patients receiving co-administered strong CYP2D6 inhibitors (e.g., quinidine, paroxetine, fluoxetine, and bupropion), the TDD of tetrabenazine should not exceed a maximum of 50 mg and the maximum single dose should not exceed 25 mg. The effect of moderate or weak CYP2D6 inhibitors such as duloxetine, terbinafine, amiodarone, or sertraline has not been evaluated.
- Patients who express CYP2D6 for extensive and intermediate metabolizers may require doses above 50 mg per day. As with lower doses, it is recommended that the dose is titrated up by 12.5 mg weekly. The TDD regimen should be given in three separate doses a day. The maximum recommended TDD is 100 mg, and the maximum recommended single dose is 37.5 mg in patients taking a TDD greater than 50 mg.
- Patients should be assessed and monitored closely for clinical worsening, suicidality, or unusual changes in behavior.

Valbenazine
- May be administered with or without food.
- The initial dose for valbenazine is 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg (two capsules) once daily. Continuation of 40 mg once daily may be considered for some patients. Dosage recommendations for patients with hepatic impairment:
  - The recommended dose for patients with moderate or severe hepatic impairment (Child-Pugh score 7 to 15) is 40 mg once daily.
- For patients at increased risk of a prolonged QT interval, assess the QT interval before increasing the dosage.
- Dosage recommendations for known CYP2D6 poor metabolizers:
  - Consider reducing dose based on tolerability for known CYP2D6 poor metabolizers.
- Coadministration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, clarithromycin):
  - Reduce dose to 40 mg once daily.
VMAT2 Inhibitors: Deutetrabenazine, Tetrabenazine, and Valbenazine

- Coadministration with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, bupropion, quinidine):
  - Consider reducing dose based on tolerability.

**Monitoring**

- Therapeutic benefit (see Inclusion Criteria).
- QTc interval, as least yearly or more often if clinically indicated (e.g., a new risk such as heart failure or myocardial infarction or other structural heart disease or if adding another medication that prolongs the QT interval).
- Mood for depression, or suicidal thoughts or behavior.
- Adverse effects such as somnolence, agitation, restlessness, akathisia, Parkinsonism.
- Abnormal Involuntary Movement Scale (AIMS).

**Issues for Consideration**

- Deutetrabenazine and valbenazine have a FDA label indication for the treatment of tardive dyskinesia.
- Deutetrabenazine and tetrabenazine have a FDA label indication for the treatment of Huntington disease chorea (See separate Criteria-for-Use).
- No minimum AIMS score is required for initiating or continuing a VMAT2 inhibitor. AIMS scores may serve as a useful tool for prescribers to quantitate the extent and severity of TD.
- Alternative approaches for the treatment of tardive dyskinesia which can be considered on a case-by-case basis:
  - Taper the dose and discontinue the offending agent, e.g., antipsychotic or metoclopramide. TD may worsen at first, and then diminish after several weeks. Little information has been published on the success of this intervention and results may be a function of the antipsychotic in question, duration of exposure and patient factors such as age and gender. Guidelines from the American Academy of Neurology state that data are insufficient to support or refute this approach to treating TD.
  - Switch the patient’s antipsychotic to a second generation (atypical) antipsychotic with a lower affinity for the dopamine-2 (D2) receptor, i.e., quetiapine or clozapine. This may not be an option for patients in whom a therapeutic response has been difficult to attain. Guidelines from the American Academy of Neurology state that data are insufficient to support or refute this approach to treating TD.
  - Amantadine is not FDA approved for the treatment of TD. Amantadine has only been studied in the treatment of tardive syndromes in conjunction with neuroleptics (flupentixol decanoate, chlorpromazine, haloperidol, trifluperazine, and thioridazine). American Academy of Neurology states that, “amantadine with neuroleptics may be considered to treat tardive syndromes for short-term use.” Amantadine was only effective in reducing dyskinesia symptoms for 7 weeks when used in conjunction with a neuroleptic.
  - Clonazepam is not FDA approved for the treatment of TD. American Academy of Neurology concludes that clonazepam is, “probably effective in decreasing tardive dyskinesia symptoms short-term (approximately 3 months) and should be considered for short-term tardive dyskinesia treatment.”
References:


2. AUSTEDO (deutetrabenazine) [prescribing information]. Teva Pharmaceuticals USA, Inc., North Wales, PA. August 2017.

3. XENAZINE (tetrabenazine) [prescribing information]. Lundbeck, Deerfield, IL. September 2018.