VMAT-2 Inhibitors (deutetrabenazine, tetrabenazine, valbenazine) for the Management of Chorea associated with Huntington Disease and Tardive Dyskinesia

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

Background: VISN 8 has requested a review of the three reversible vesicular monoamine transporter-2 (VMAT-2) inhibitors, with specific interest in the ability to sequence these agents. VMAT-2 is located on synaptic vesicles of dopamine, norepinephrine, serotonin, and histamine.[22] Inhibition of VMAT-2 regulates the uptake of monoamines in the central nervous system and results in monoamine depletion. The VMAT-2 inhibitors are utilized for the management of chorea associated with Huntington Disease (HD) and for the management of tardive dyskinesia (TD). Tetrabenazine, the first VMAT-2 inhibitor, was approved in 2008 for Huntington's chorea and is used off-label for the treatment of TD. Deutetrabenazine and valbenazine were FDA approved in 2017. Currently, deutetrabenazine, tetrabenazine, and valbenazine are non-formulary drugs with separate CFU. The goal of this review is to provide an overview of this class of medication for the Committee to review. Comparative information is summarized in the tables below.

Contents:

Table 1. General Information

	Deutetrabenazine	Tetrabenazine	Valbenazine
Dosage Form (Formulary Status)	Tablets, oral: 6 mg, 9 mg, 12 mg (NF)	Tablets, oral: 12.5 mg, 25 mg (NF)	Capsule, oral: 40 mg, 60 mg, 80mg (NF)
Administration	Administer with food. Swallow tablets whole, not crushed, chewed, or broken	May administer without regard to meals	Administer with or without food
Indication	Chorea associated with Huntington disease, Tardive dyskinesia	Chorea associated with Huntington disease	Tardive dyskinesia
Contraindications	• Suicidal/untreated depression, • Hepatic impairment • Taking reserpine • Taking MAOI • Taking another VMAT-2 inhibitor	• Suicidal/untreated depression • Hepatic impairment • Taking reserpine • Taking MAOI • Taking another VMAT-2 inhibitor	• Hypersensitivity to valbenazine
Half-life	9-10 hours	5-7 hours	15-22 hours

MAOI, monoamine oxidase inhibitor

Table 2. Dosage: Chorea associated with Huntington disease

Deutetrabenazine	6 mg once daily; may increase dose weekly based on response and tolerability in increments of 6 mg/day; administer in two divided doses if total daily dose ≥12 mg; maximum recommended dose: 48 mg/day
Tetrabenazine	12.5 mg once daily in the morning, may increase to 12.5 mg twice daily after 1 week. Dosage may be increased by 12.5 mg daily at weekly intervals; daily doses >37.5 mg should be divided into 3 doses (maximum single dose: 25 mg). Patients requiring doses >50 mg/day should be genotyped for CYP2D6
Valbenazine	N/A

N/A, not applicable

Table 3. Dosage: Tardive Dyskinesia

Deutetrabenazine	6 mg twice daily; may increase dose weekly based on response and tolerability in increments of 6 mg/day. Administer in two divided doses if total daily dose ≥12 mg; maximum recommended dose: 48 mg/day.
Tetrabenazine	**Off-label:** 12.5 mg daily for one week and increased by 12.5 mg increments every few days, according to clinical response and as tolerated, to a usual effective dose of 75 to 150 mg daily. Daily doses >37.5 mg should be divided into three doses. The maximum recommended single and daily doses are lower (25 and 50 mg, respectively) for patients taking strong CYP2D6 inhibitors
Valbenazine	40 mg once daily; after 1 week, increase to 80 mg once daily. Continuation of 40 or 60 mg once daily may be considered for some patients based on response and tolerability

Table 4. Efficacy: Deutetrabenazine, tardive dyskinesia [7,13,14]

Study	**Study design**	**Primary endpoint**	**Efficacy Results**
AIM-TD trial/Study 1 (N=298) Mean baseline AIMS score ranged from 9.4 to 10.1	12-week randomized, double-blind study	Change in AIMS score from baseline to week 12	DBZ reduced LSM AIMS scores from baseline to week 12 vs. PBO 36 mg; –3.3 vs.–1.4, p=0.001, 24 mg; -3.2 vs -1.4, p=0.003, 12 mg; -2.1 vs -1.4, p=0.22
ARM-TD trial/Study 2 (N=117) Mean baseline AIMS Score=9.6	12-week, randomized, double-blind, parallel-group study	Change in AIMS score from baseline to week 12	DBZ reduced LSM AIMS scores from baseline to week 12 vs. PBO (–3.0 vs.–1.6, p=0.019).

AIMS, Abnormal Involuntary Movement Scale; LSM, least-squares mean; DBZ, deutetrabenazine

Table 5. Efficacy: Deutetrabenazine, Huntington's Disease [7]

Study	**Study design**	**Primary endpoint**	**Efficacy Results**
Study 1 (N=90)	12-week, randomized, double-blind, placebo-controlled, multi-center	Change in Total Chorea Score from baseline to maintenance therapy	DBZ -4.4 vs. placebo -1.9, p<0.0001

DBZ, deutetrabenazine

Table 6. Efficacy: Tetrabenazine, tardive dyskinesia [12]

Study	Study design	Primary Outcome
Godwin-Austen and Clark (N=6)	Randomized, double-blind, crossover	3/6 improved with absence of movement
Kazamatsuri et al (N=13)	18-week, randomized, placebo-controlled	2/6 with 100% disappearance of abnormal movements
Asher and Aminoff (N=10)	3-week, single-blind, placebo-controlled, crossover	6/10 with marked or moderate improvement
Jankovic (N=4)	Randomized, double-blind, placebo-controlled, crossover	4/4 improved

Table 7. Efficacy: Tetrabenazine, Huntington's Disease [17]

Study	Study design	Primary endpoint	Efficacy Results
Study 1/TETRA-HD (N=84)	12-week, randomized, double-blind, placebo-controlled, multi-center	Change in Total Chorea Score from baseline to average of weeks 9 and 12	TBZ -5.0 vs. placebo -1.5, p=0.0001

TBZ, tetrabenazine

Table 8. Efficacy: Valbenazine, tardive dyskinesia [9,15,16]

Study	Study design	Primary endpoint	Efficacy Results
KINECT 2 (N=205)	6-week, randomized, double-blind, placebo-controlled, dose-titration	Change in AIMS score from baseline to week 6	VBZ reduced LSM AIMS scores from baseline to week 6 vs. PBO -2.6 vs. -0.2, p=0.0005
KINECT 3 (N=225)	6-week, randomized, double-blind, placebo-controlled	Change in AIMS score from baseline to week 6	VBZ reduced LSM AIMS scores from baseline to week 6 vs. PBO 80 mg; –3.2 vs.–0.1, p<0.001, 40 mg; - 1.9 vs -0.1, p=0.002

AIMS, Abnormal Involuntary Movement Scale; LSM, least-squares mean; VBZ, valbenazine

Table 9. Safety – Adverse Reactions [7-9]

Drug	Side effects
Deutetrabenazine	HD: somnolence, diarrhea, dry mouth, fatigue, insomnia TD: insomnia, nasopharyngitis, depression, akathisia
Tetrabenazine	HD: somnolence, insomnia, fatigue, depression, akathisia, anxiety
Valbenazine	TD: somnolence, dry mouth, dizziness, headache, akathisia

HD, Huntington's Disease; TD, Tardive Dyskinesia

Table 10. Warnings and Precautions [7-9]

	DBZ	TBZ	VBZ
Depression and suicidality**	X	X	
Neuroleptic malignant syndrome	X	X	
Akathisia, restlessness, agitation	X	X	
Parkinsonism	X	X	X
Sedation and somnolence	X	X	X
QTc prolongation	X	X	X
Hypotension and orthostatic hypotension		X	
Hyperprolactinemia	X	X	
Binding to melanin-containing tissues	X	X	

** box warning; DBZ, deutetrabenazine, TBZ, tetrabenazine; VBZ, valbenazine

Table 11. Significant Drug Interactions [7-9]

	DBZ	TBZ	VBZ
Strong CYP2D6 inhibitors	X	X	X
Reserpine	X	X	
MAOI	X	X	X
Alcohol/Sedating drugs	X	X	
Drugs causing QTc prolongation		X	
Neuroleptic drugs	X	X	
Concomitant VMAT-2 inhibitors	X	X	
Strong CYP3A4 inhibitors			X
Strong CYP3A4 inducers			X
Digoxin			X

MAOI, monoamine oxidase inhibitor; DBZ, deutetrabenazine, TBZ, tetrabenazine; VBZ, valbenazine

Table 12. Utilization: Drug Induced Subacute Dyskinesia (e.g., TD)

	CY19-CY21				
	Pts on Rx	Pts on Dx			
Rx	Pts on Rx	Pts with Drug Induced Subacute Dyskinesia	Pts on Rx w/ Dx	% Dx pts on Rx	% Rx pts having Dx
		6,685			
DBZ	388		219	3.28	56.44
TBZ	793		351	5.25	44.26
VBZ	757		509	7.61	67.24
ALL RXs	1,754		948	14.18	54.05

DBZ, deutetrabenazine, TBZ, tetrabenazine; VBZ, valbenazine

Table 13. Utilization: Huntington Disease

	CY19-CY21				
	Pts on Rx	Pts on Dx			
Rx	Pts on Rx	Pts with Huntington Disease	Pts on Rx w/ Dx	% Dx pts on Rx	% Rx pts having Dx
		1,137			
DBZ	388		67	5.89	17.27
TBZ	793		167	14.69	21.06
VBZ	757		6	0.53	0.79
All RXs	1,754		223	19.61	12.71

DBZ, deutetrabenazine, TBZ, tetrabenazine; VBZ, valbenazine

Table 14. Utilizations: Drug Induced Subacute Dyskinesia (TD) OR Huntington Disease

	CY19-CY21				
	Pts on Rx	Pts on Dx			
Rx	Pts on Rx	Pts with Drug induced subacute dyskinesia OR Huntington disease	Pts on Rx w/ Dx	% Dx pts on Rx	% Rx pts having Dx
		7,810			
DBZ	388		285	3.65	73.45
TBZ	793		515	6.59	64.94
VBZ	757		514	6.58	67.90
All RXs	1,754		1,166	14.93	66.48

DBZ, deutetrabenazine, TBZ, tetrabenazine; VBZ, valbenazine

Proposed Place in Therapy and Formulary Considerations

Huntington disease (HD) is an inherited progressive neurodegenerative disorder characterized by choreiform movements, psychiatric problems, and dementia. The VMAT-2 inhibitors, tetrabenazine and deutetrabenazine, are utilized to reduce chorea associated with HD. Valbenazine is not approved for HD related chorea. A review of the evidence suggests that TBZ and DBZ have similar efficacy. Differences lay in dosing frequency, genotyping, and cost, with indirect evidence suggesting better tolerability with DBZ.[19,20] In general, the indirect evidence is not supported by VA ADERS information. Usage data suggest that TBZ is the workhorse agent followed by DBZ and VBZ. Sequencing does not appear to be warranted.

Tardive dyskinesia is a medication induced movement disorder associated with the use of dopamine receptor antagonist (e.g., antipsychotics, metoclopramide). While all three VMAT-2 inhibitors are used to manage TD, only DBZ and VBZ are FDA approved. A review of the evidence suggests that DBZ and VBZ differ in dosing frequency, contraindications, warning/precautions (e.g., depression/suicidality), drug interactions, and cost. VA ADERS information shows ADE per 10,000 unique patients to be higher with VBZ compared to DBZ for FY 2021 and FY 2022. Utilization data shows that the majority are patients with TD are receiving VBZ followed by TBZ and DBZ respectively. Given the lack of head-to-head trials among the VMAT-2 inhibitors, multiple systematic reviews, and meta-analyses, have been conducted. [4-6] Both deutetrabenazine and valbenazine have been found to have similar efficacy in reducing Abnormal Involuntary Movement Scale scores with similar tolerability. There is a lack of high-quality data for tetrabenazine in the management of tardive dyskinesia.

The use of antipsychotics, potentially causing TD, in the treatment of major depressive disorder (MDD) is likely to be high. Mohamed and colleagues reported that 20.6% of Veterans with MDD received antipsychotic medications, many of whom received them at the higher doses recommended for schizophrenia.[23] Without conducting a chart review, to determine if depression/suicidality, a

contraindication to DBZ and TBZ, was the reason for VBZ initiation, it is difficult to know if DBZ or TBZ could be used in placed of VBZ. Further, drug-drug interactions and medical conditions (e.g., hepatic impairment) may impact choice of VMAT-2 inhibitor for the management of TD. There is insufficient data to support sequencing of VMAT-2 inhibitors for the management of TD.

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