Drug Watch Deutetrabenazine¹

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ABSTRACT

Deutetrabenazine is indicated in the management of chorea associated with Huntington's disease and in the treatment of Tardive dyskinesia in adults by US FDA. However, it should be used with a pinch of salt, as it can raise the risk of depression and suicidal thoughts with unusual behavioural abnormalities specially in patients with Huntington's disease. The family history is an added risk factor and close monitoring is required and the molecule is contraindicated in this group of patients. In hepatic impairment it is also not recommended. It shouldn't be used with Reserpine. A window period of 3 weeks after discontinuation of reserpine and 2 weeks for MAO inhibitors and tetrabenazine or valbenazine is recommended.

Keyword : Deutetrabenazine, VMAT2 inhibitor, Huntington's disease, Tardive dyskinesia.

Deutetrabenazine (AUSTEDO; Teva Neuroscience, Inc. AUS-41689, April 2019) is a vesicular

monoamine transporter 2 (VMAT 2) inhibitor for oral administration.¹ The chemical structure is shown in Figure 1. The tablet is available in following strengths 6 mg, 9 mg and 12 mg. The precise mechanism of action is not known but believed to be a reversible depletion of monoamines (e.g dopamine, serotonin, noradrenalines, histamines etc.) from

nerve terminals. The major active metabolites alpha and beta-dihydrodeutetrabenazine (HTBZ) of

Deutetrabenazine

Fig 1 : Chemical Structure of Deutetrabenazine.

Figure 2: Mechanism of action of Deutetrabenazine.

deutetrabenazine is a reversible inhibitor of VMAT² resulting in decreased uptake of monoamines in the synaptic vesicles leading to depletion of monoamine stores. VMAT inhibition helps to regulate dopamine function. Some vesicular monoamine transporter 2 (VMAT2) inhibitors reduce available dopamine via alpha and/or beta metabolites that block sequestration in the presynaptic vesicle (Figure 2). 2 Unsequestered dopamine is degraded by monoamine oxidase.^{3,4} Reducing dopamine levels in the presynaptic neuron results in less dopamine signaling to the postsynaptic neuron, leading to fewer abnormal involuntary movements.²⁻⁴

Pharmacodynamics : Summarized in Table 1.

Table 1 : Pharmacodynamics of Deutetrabenazine

Cardiac electrophysiology	In a DBRPCT, the cardiac effect on QTc interval studied of a single dose 12 & 24 mg respectively with moxifloxacin as positive control. At a dose of 24 mg/d the mean increase of QTc is 4.5 msec (90% CI : 2.4, 6.5 msec).
Melanin binding	Deutetrabenazine and its active metabolites bind to melanin containing tissues (e.g eye, skin, fur) in pigmented rats. Human studies to be evaluated further.

Pharmacokinetics : It goes extensive fast pass metabolism to active deuterated dihydrometabolites in the liver. The exposure is 40% greater in the patients with hepatic impairment. Linear dose response curve is being observed. About 80% of the molecule is absorbed. Plasma concentration of the molecule is below detection level. Peak plasma concentration (C_{max}) is reached within 3-4 hours of

dosing. Food has no effect with its absorption, AUC but C_{max} is increased by 50% in presence of food. It is primarily eliminated via kidney in the form of metabolites. The t_{1/2} of alpha and beta HTBZ combined is 9-10 hours. The active metabolites are finally get metabolized primarily by CYP2D6 and also in insignificant way secondarily via CYP1A2, CYP3A4/5 pathways. 75-86% of deutetrabenazine is excreted in urine.

Drug interactions : (i) With CYP2D6 inhibitors- Paroxetine decreases the clearance of active metabolites with increase in mean half-life. The dose adjustment is necessary to avoid adverse effects and/or toxicity. (ii) Digoxin is a substrate of P-glycoprotein. The bioavailability of digoxin was not changed when co-prescribed with tetrabenazine/ deutetrabenazine.

Summary of clinical trials : Mentioned in Table 2.

Table 2 : Summary of clinical trials of Deutetrabenazine

Disease	Summary of primary outcome measures
1. Chorea associated with Huntington's disease	Significant reduction of TMC (Total maximum chorea score) score in comparison to placebo (P< 0.0001)
2. Tardive dyskinesia	Significant reduction in AIMS score (Higher dose 36 mg/d works better than lower dose 12 mg/d over 12 weeks (Treatment effect with 95% CI : -1.9 (-3.09, -0.79)

Adverse effects : Most common side effects that are being observed are nasopharyngitis, insomnia, somnolence, dry mouth, fatigue, urinary tract infections, anxiety, depression, dysthymia, akathisia, agitation, restlessness constipation, confusions etc which are mostly benign.

Special populations : No adequate data on its safety in pregnancy, lactation and in paediatric or geriatric population (dose adjustment is necessary).

Dosage and administration : Summarized in Table 3.

Table 3 : The recommended dosage guideline by USFDA.

Disease	Initial dose	Recommended dose	Maximum dose
Chorea associated with Huntington's disease	6 mg/d	6-48 mg/d	48 mg/d
Tardive dyskinesia in adults	12 mg/d	12-48 mg/d	48 mg/d

The dose has to be titrated at weekly intervals by 6 mg/d based on reduction of chorea and tardive dyskinesia, patient's tolerability upto a maximum tolerable dose 48 mg/d (24 mg BD). If the total

daily dose is equal or more than 12 mg/d, it should be given in BD dose. The patients at risk should be monitored by doing an ECG before and after increasing the total dose 24mg or above per day.

Caution : Following cautions as summarized in Table 4 has to be maintained.

Table 4 : Cautions while prescribing Deutetrabenazine

1. Depression and suicidality in patients of Huntington's disease(HD)	2. Clinical worsening of adverse events in patients of HD.	3. QTc prolongation.
4. Neuroleptic malignant syndrome (NMS)	5. Akathisia, agitation and restlessness.	6. Parkinsonism in patients of HD.
7. Sedation and somnolence.	8. Hyperprolactinemia.	9. Binding to melanin containing tissues.

The guideline of switching from Tetrabenazine to Deutetrabenazine is summarized on Table 5.

Table 5 : FDA recommended dose for switching from Tetrabenazine to Deutetrabenazine.

Current daily dosage of Tetrabenazine	Recommended initial dose of Deutetrabenazine (AUSTEDO)
12.5 mg	6 mg od
25 mg	6 mg bd
37.5 mg	9 mg bd
50 mg	12 mg bd
62.5 mg	15 mg bd
75 mg	18 mg bd
87.5 mg	21 mg bd
100 mg	24 mg bd

REFERENCES

1. https://www.austedo.com/huntingtons-chorea?gclid=CjwKCAjw5pPnBRBJEiwAULZKvh1sTvNlf2WjOpWdlSS6eEATlaxM89WxENG_wfxjH5CZq2yvPb5-5hoCot0QAvD_BwE & gclsrc = aw.ds last accessed on 22/05/2019.
2. AUSTEDO® (deutetrabenazine) tablets Prescribing Information. Teva Pharmaceuticals USA, Inc. August 2017.
3. Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia : the ARM-TD study. *Neurology*. 2017; 88(21) : 2003-2010.
4. Data on file. Teva Neuroscience, Inc. 4. Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD) : a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Psychiatry*. 2017; 4(8) : 595-604.