CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
1Q18 January – February

BRAND NAME
Austedo™

GENERIC NAME
Deutetrabenazine

MANUFACTURER
Teva Pharmaceuticals USA, Inc.

DATE OF APPROVAL
August 30, 2017

PRODUCT LAUNCH DATE
Currently commercially available

REVIEW TYPE
☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)[1]
New/Revised Indication(s)
Treatment of tardive dyskinesia in adults

Current Indication(s)
Treatment of chorea associated with Huntington's disease

OFF LABEL USES
Tourette's syndrome

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CLINICAL EFFICACY

Background

Tardive dyskinesia is a movement disorder resulting from exposure to dopamine receptor blocking agents (DRBAs), such as antipsychotics. Withdrawal of the offending DRBAs is not always be possible due to risk of psychotic relapse. Even if withdrawal is possible, it still may not successfully reverse dyskinesia symptoms and may actually increase symptoms acutely. There have been a number of therapies, such as amantadine, tetrabenazine, clonazepam, levetirecetam, and botulinumtoxinA, which have been used off-label for the treatment of tardive dyskinesia; however, none have clearly established efficacy (i.e., Level A recommendation) per the American Academy of Neurology 2013 tardive dyskinesia guidelines.[2]

Austedo is a newly approved vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of tardive dyskinesia. The only other drug FDA-approved for this use is Ingrezza (valbenazine), another VMAT2 inhibitor approved in April 2017.

The precise mechanism by which Austedo exerts its effects in the treatment of tardive dyskinesia is unknown but is believed to be related to its effect as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals.

<table>
<tr><th></th><th>Fernandez HH, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia: the ARM-TD study[3]</th></tr>
<tr><td>Study Design</td><td>12-week, randomized (1:1), double-blind, parallel-group, multicenter phase 2/3 trial</td></tr>
<tr><td>N</td><td>117</td></tr>
<tr><td>Drug Regimen</td><td>Austedo 12 mg/day, titrated weekly by 6 mg/day as needed for up to 6 weeks up to a maximum of 48 mg/day (n=58)* or matching placebo (n=59)
*The mean total daily dose at the end of the titration period was 38.8 mg/day. This remained stable until the end of the treatment period (38.3 mg/day).</td></tr>
<tr><td>Primary Outcome(s)</td><td>Change in Abnormal Involuntary Movement Scale (AIMS) score from baseline to week 12 as assessed by 2 blinded central video raters who were movement disorders experts</td></tr>
<tr><td>Secondary Outcome(s)</td><td>• Proportion of patients who experienced treatment success at week 12 defined as a rating of “much improved” or “very much improved” on the:
o Clinical Global Impression of Change (CGIC)
o Patient Global Impression of Change (PGIC)
• Change from baseline in the modified Craniocervical Dystonia Questionnaire (mCDQ-24)</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Outcome</th><th>Austedo</th><th>Placebo</th><th>Difference</th><th>P-value/95% CI</th></tr>
<tr><td>AIMS, mean change (standard error [SE])</td><td>-3.0 (0.45)</td><td>-1.6 (0.46)</td><td>-1.4* (0.60)</td><td>p = 0.019
95% CI -2.6, -0.2</td></tr>
<tr><td>CGIC, %</td><td>48.2</td><td>40.4</td><td colspan="2">Not statistically significant</td></tr>
<tr><td>PGIC, %</td><td>42.9</td><td>29.8</td><td colspan="2">Not statistically significant</td></tr>
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<tr><td></td><td>
<table>
<tr><td>mCDQ-24, mean change (SE)</td><td>-11.1 (2.14)</td><td>-8.3 (2.31)</td><td>Not statistically significant</td></tr>
</table>
Improvement was different between both groups by week 4.
</td></tr>
<tr><td># Withdrew due to Lack of Efficacy</td><td>No patients in both groups</td></tr>
<tr><td># Withdrew due to Adverse Effects</td><td>• Austedo: 1 patient
• Placebo: 2 patients</td></tr>
<tr><td></td><td>Anderson KE, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial[4]</td></tr>
<tr><td>Study Design</td><td>12-week, randomized (1:1:1:1), double-blind, parallel-controlled, multicenter phase 3 trial</td></tr>
<tr><td>N</td><td>298</td></tr>
<tr><td>Drug Regimen</td><td>Austedo (12 mg/day [n=75], 24 mg/day [n=74], or 36 mg/day [n=75])* or placebo (n=74)
*Patients were started at 12 mg/day; the dose was increased weekly by 6 mg/day to the randomized dose during the first 4 weeks. Dose reduction by 6 mg/day once in the 8 weeks that followed was allowed for patients who had clinically significant adverse events; 1 patient receiving 24 mg/day and 3 patients receiving 36 mg/day required dose reduction.</td></tr>
<tr><td>Primary Outcome(s)</td><td>Change in AIMS score from baseline to week 12 as assessed by 2 blinded central video raters who were movement disorders experts</td></tr>
<tr><td>Secondary Outcome(s)</td><td>• Proportion of patients who had investigator-assessed treatment success at week 12 defined as a rating of “much improved” or “very much improved” on the CGIC
• Change in CGIC from baseline at week 12
• Proportion of AIMS responders (10-90% improvement in AIMS score), with an improvement of ≥ 50% being clinically significant
• Difference in mCDQ-24 from baseline to week 12
• Proportion of patients with treatment success as measured by PGIC</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Outcome</th><th>Austedo 12 mg/day</th><th>Austedo 24 mg/day</th><th>Austedo 36 mg/day</th><th>Placebo</th></tr>
<tr><td>AIMS, mean change (SE)*</td><td>-2.1 (0.42)</td><td>-3.2 (0.45)</td><td>-3.3 (0.42)</td><td>-1.4 (0.41)</td></tr>
<tr><td>Difference vs placebo (p-value; 95% CI)</td><td>-0.7 (0.217; -1.84, 0.42)</td><td>-1.8 (0.003; -3, -0.63)</td><td>-1.9 (0.001; -3.09, -0.79)</td><td>---</td></tr>
<tr><td>Proportion with ≥ 50% improvement (odds ratio [OR]; p-value; 95% CI)**</td><td>Not provided</td><td>35% (3.96; 0.005; 2.46, 10.72)</td><td>33% (3.8; 0.007; 1.4, 10.36)</td><td>12%</td></tr>
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	Proportion with treatment success on CGIC (p-value)	28% (0.734)	49% (0.014)	44% (0.059)	26%
	Difference in CGIC, mean (SE; p-value, 95% CI)	Not provided	-0.6 (0.20; 0.002; -0.99, -0.22)	-0.5 (0.19; 0.011; -0.86, -0.12)	---
	**Response was observed by week 2 for patients in the Austedo 24 mg/day and 36 mg/day groups.* ***More patients had statistically significant response at 10-70% AIMS improvement in the Austedo 24 mg/day and 36 mg/day groups, and at 80% in the Austedo 36 mg/day group, compared to placebo. 90% improvement with Austedo 36 mg/day was not statistically significant.* In addition, patients receiving Austedo 24 mg/day and 36 mg/day had numerically better responses on mCDQ-24 and PGIC, but these results were not significant.				
# Withdrew due to Lack of Efficacy	No patients in all groups				
# Withdrew due to Adverse Effects	• Austedo: 9 patients o 4 received 12 mg/day, 2 received 24 mg/day, 3 received 36 mg/day • Placebo: 2 patients				

CONTRAINDICATIONS
Austedo is contraindicated in patients:
- With Huntington's disease who are suicidal or have untreated/inadequately treated depression,
- With hepatic impairment, and
- Taking reserpine, monoamine oxidase inhibitors (MAOIs), tetrabenazine, or valbenazine.

BLACK BOX WARNINGS
Austedo has a black box warning for increased risk of depression and suicidality in patients with Huntington's disease. In a 12-week, double-blind, placebo-controlled trial, suicidal ideation was reported by 2% of patients treated with Austedo, compared to no patients on placebo; no suicide attempts and no completed suicides were reported. Depression was reported by 4% of patients treated with Austedo.

DRUG INTERACTIONS
- Strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, bupropion): Strong CYP2D6 inhibitors can increase systemic exposure to Austedo. The maximum recommended dose of Austedo when used concomitantly with strong CYP2D6 inhibitors is 36 mg per day (18 mg twice daily).

- QT prolonging drugs (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone, moxifloxacin, quinidine, procaindamide, amiodarone, sotalol): Austedo can increase QT interval. Patients requiring doses of Austedo above 24 mg who are taking QT prolonging drugs should be evaluated before and after any dose increases.
- Reserpine: Reserpine binds irreversibly to VMAT2 and the duration of its effect is several days. Provider should not administer Austedo until symptoms of dyskinesia remerge in order to reduce the risk of overdosage and major depletion of serotonin and norepinephrine in the central nervous system. At least 20 days should elapse after stopping reserpine before starting Austedo, and they should not be used concomitantly.
- MAOIs: Austedo is contraindicated in patients taking MAOIs. Austedo should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI.
- Neuroleptic drugs: Concomitant use with dopamine antagonists or antipsychotics may increase the risk of parkinsonism, neuroleptic malignant syndrome, and akathisia.
- Alcohol or other sedating drugs: Concomitant use may have additive sedation and somnolence.
- Tetrabenazine or valbenazine: These drugs are in the same therapeutic class as Austedo (VMAT inhibitor).

ADVERSE REACTIONS
The most common adverse reactions (occurred in 4% of Austedo-treated patients with tardive dyskinesia and greater than placebo) are nasopharyngitis and insomnia.

In addition, Austedo has warnings for QT prolongation, neuroleptic malignant syndrome, akathisia, agitation, restlessness, parkinsonism, and sedation/somnolence.

DOSAGE AND ADMINISTRATION
The initial dose of Austedo in tardive dyskinesia is 12 mg/day orally, titrated by 6 mg/day at weekly intervals based on reduction of tardive dyskinesia and tolerability up to a maximum of 48 mg/day (maximum of 36 mg/day if a poor CYP2D6 metabolizer or concurrently receiving strong CYP2D6 inhibitors). Doses ≥ 12 mg should be administered in two divided doses.

PRODUCT AVAILABILITY
Tablets: 6 mg, 9 mg, 12 mg

THERAPEUTIC ALTERNATIVES[2, 5]

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Ingrezza™ (valbenazine)	40 mg PO QD, increased to 80 mg PO QD after 1 week	• FDA-approved • VMAT2 inhibitor
clonazepam (Klonopin®)	Up to 4.5 mg PO QD	• Off-label • AAN level B recommendation for

		short-term use (3 months) • Not in DrugDex
amantadine	300 mg/day PO	• Off-label • AAN level C recommendation for short-term use with neuroleptics (7 weeks) • DrugDex class III recommendation
tetrabenazine (Xenazine®)	Up to 200 mg/day PO	• Off-label • AAN level C recommendation • DrugDex class IIb recommendation
levetiracetam (Keppra®)	Up to 3000 mg/day PO	• Off-label • AAN level U recommendation (insufficient to recommend) • Not in DrugDex
Botox® (onabotulinumtoxinA)	For oro-facial-lingual-masticatory tardive dyskinesia: 80 units SQ into 4 facial sites (lateral to buccal commissures, midpoint of upper lip, mid-central area of chin)	• Off-label • AAN level U recommendation (insufficient to support or refute) • DrugDex class IIb recommendation

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be considered for the following reason(s):
  - ☒ Opportunity exists to obtain clinically significant medical or laboratory information necessary to determine appropriate use of the medication.
    - i) Austedo is indicated for tardive dyskinesia, which is secondary to DRBAs.
    - ii) Recommended utilization management tool(s): (check all that apply)
      - (1) ☒ Prior authorization
      - (2) ☐ Quantity limits
      - (3) ☐ Provider newsletter
      - (4) ☐ Hard block (plan exclusion)
      - (5) ☐ Messaging

(6) ☐ Electronic step therapy
(7) ☐ Clinical program

iii) Austedo currently requires a PA; recommend to maintain PA status.

Product Comparison

- Equal therapeutic outcomes are anticipated for Austedo and Ingrezza; therefore, it would be clinically appropriate to provide equal access to both or to require a trial of one before the other.
- It would be clinically appropriate to provide equal access to Austedo and drugs used off-label for tardive dyskinesia (e.g., clonazepam, amantadine, tetrabenazine, levetiracetam, and botulinum toxin); however, it would not be appropriate to require any off-label drugs prior to initiation of Austedo.

REFERENCES

[1] Austedo Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; August 2017. Available at https://www.austedo.com. Accessed September 18, 2017
[2] Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: Treatment of tardive syndromes. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013; 31: 463-469.
[3] Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia: The ARM-TD study. Neurology. 2017; 88: 1-8.
[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.
[5] DrugDex® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed September 18, 2017.