CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
3Q17 July – August

BRAND NAME
Ingrezza™

GENERIC NAME
Valbenazine

MANUFACTURER
Neurocrine Biosciences, Inc.
San Diego, CA 92130

DATE OF APPROVAL
April 11, 2017

PRODUCT LAUNCH DATE
First week in May 2017

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 Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION
Ingrezza is indicated for the treatment of adults with tardive dyskinesia.

OFF-LABEL USES
None found.

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CLINICAL EFFICACY

The efficacy of Ingrezza was assessed in a randomized, double-blind, placebo-controlled trial conducted in patients with moderate to severe tardive dyskinesia as determined by clinical observation. A total of 234 subjects were enrolled, with 29 (12%) discontinuing prior to completion of the placebo controlled period. Patients had underlying schizophrenia, schizoaffective disorder, or a mood disorder. With respect to concurrent antipsychotic use, 70% of subjects were receiving atypical antipsychotics, 14% were receiving typical or combination antipsychotics, and 16% were not receiving antipsychotics. Individuals at significant risk for suicidal or violent behavior and individuals with unstable psychiatric symptoms were excluded.

The primary efficacy endpoint was the mean change from baseline in the Abnormal Involuntary Movement Scale (AIMS) dyskinesia total score at the end of Week 6. The change from baseline for two fixed doses of Ingrezza (40 or 80 mg) was compared to placebo. At the end of Week 6, subjects initially assigned to placebo were re-randomized to receive Ingrezza 40 mg or 80 mg. Subjects originally randomized to Ingrezza continued Ingrezza at their randomized dose. Follow-up was continued through Week 48 on the assigned drug followed by a 4-week period off-drug. The change from baseline in the AIMS total dyskinesia score in the 80 mg Ingrezza group at Week 6 was significantly different from the change in the placebo group (placebo-subtracted difference ([95% CI] -3.1 [-4.2, -2.0]).[1,3]

CONTRAINDICATIONS

None reported.

BLACK BOX WARNINGS

None reported.

DRUG INTERACTIONS

- MAOIs: Avoid concomitant use.
- Strong CYP3A4 inducers: Concomitant use is not recommended
- Strong CYP3A4 inhibitors: Reduce dose to 40 mg.
- Strong CYP2D6 inhibitors: Consider dose reduction based on tolerability.
- Digoxin: If concomitant administration, digoxin levels should be monitored.

ADVERSE REACTIONS

Most common adverse reactions (≥5% and twice the rate of placebo): Somnolence. Patients should not perform activities requiring mental alertness such as operating a motor vehicle or operating hazardous machinery until they know how they will be affected by Ingrezza.[1]

DOSAGE AND ADMINISTRATION

- Initial dose: 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily. Continuation of 40 mg once daily may be considered for some patients.[1]
- Administer Ingrezza orally with or without food.[1]

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PRODUCT AVAILABILITY
Ingrezza oral tablets: 40 mg

THERAPEUTIC ALTERNATIVES
Deutetrabenazine: Labeled use (Huntington's chorea): Initial dose of 6 mg daily. Dose is titrated upward for reduction of symptoms if needed. Doses ≥ 12 mg are divided. Maximum dose is 48 mg daily in divided doses.[2] In the ARM-TD trial, initial dose was higher at 6 mg BID; all else per labeled dosing.[4]

Utilization Management Recommendation
1) There is significant potential for inappropriate use and utilization management should be considered for the following reasons: a) To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes: i) Ingrezza is indicated for tardive dyskinesia (dyskinesia secondary to centrally acting dopamine-receptor blocking agents). 2) 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
Product Comparison
○ Equal therapeutic outcomes are anticipated for Ingrezza and Austedo. ○ It would not be clinically appropriate to require a trial of Austedo prior to Ingrezza until Austedo receives FDA approval for tardive dyskinesia. ○ It would not be appropriate to require any other drugs, including the following drugs, prior to Ingrezza: ▪ Clonazepam • American Academy of Neurology[5] (AAN) Level B for short-term use ▪ Amantadine • AAN Level C for short-term use with neuroleptics ▪ Tetrabenazine • AAN Level C

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- Botulinum toxin type A
  - AAN Level U
- Levetiracetam
  - AAN Level U

REFERENCES

1. Ingrezza Prescribing Information. San Diego, CA: Neurocrine Biosciences, Inc.; April 2017. Available at: http://ingrezza.com/PI. Accessed May 12, 2017.
2. Austedo Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; April 2017. Available at https://www.austedo.com/pi. Accessed May 12, 2017.
3. Hauser RA, Factor SA, Marder SR. KINECT 3: A phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry*. May 1, 2017; 174(5): 476-484. doi: 10.1176/appi.ajp.2017.16091037. Epub 2017 Mar 21.
4. 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.
5. 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.