Drug Monograph

Drug/Drug Class:	**Brintellix™ (vortioxetine hydrobromide) Tablets/ serotonergic antidepressant**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each 5 mg, 10 mg, 15 mg and 20 mg immediate release tablet contains 5 mg, 10 mg, 15 mg and 20 mg respectively of vortioxetine hydrobromide. Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015
Summary of Findings:	Brintellix is a serotonergic antidepressant indicated for the treatment of major depressive disorder.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Fiscal Edit ☒ Clinical Edit
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Major depressive disorder is a condition that plagues nearly 14.8 million American adults and is the leading cause of disability in the United States for ages 15-44. MDD can be difficult to treat and is often strongly related to comorbidity.

Dosage Form(s)[1]

Each 5 mg, 10 mg, 15 mg and 20 mg immediate release tablet of Brintellix contains 5 mg, 10 mg, 15 mg and 20 mg respectively of vortioxetine hydrobromide.

Manufacturer

Takeda Pharmaceuticals America, Inc., Deerfield, IL 60015

Indication(s)[1]

Brintellix is indicated for the treatment of major depressive disorder.

Clinical Efficacy[1] (mechanism of action/pharmacology, comparative efficacy)

Brintellix is a serotonergic antidepressant which inhibits the reuptake of serotonin (5-HT), antagonizes 5-HT3, 5-HT1D, and 5-HT7 receptors, is an agonist at 5-HT1A receptors, and is a partial agonist of the 5-HT1B receptor. Although the mechanism of action has not been clearly defined, activity at the serotonin receptor subtypes is felt to be related to the clinical antidepressant effects of Brintellix.

	BRINTELLIX
Protein binding	98%
Volume of distribution	2600 L
Metabolism	Hepatic, primarily via CYP2D6
Excretion	Urine (59%, as metabolites)
Half-life	Feces (26%, as metabolites)

Brintellix was evaluated in 6 double-blind, randomized, placebo-controlled trials for the treatment of major depressive disorder, one of which was in elderly patients. In each trial, patients who received Brintellix experienced greater improvements in symptoms compared with patients who received placebo. Brintellix also demonstrated efficacy as maintenance treatment in an open-label, placebo-controlled clinical trial by achieving a significantly longer time to

recurrence of depressive episodes compared with placebo. Brintellix has not been evaluated in comparison with other antidepressant agents.

MAJOR DEPRESSIVE DISORDER - ADULT PATIENTS – Study 1

STUDY DESIGN	Five 6 to 8-week, randomized, placebo-controlled studies (n=2090).
INCLUSION CRITERIA	Adults, 18 to 75 years of age, with major depressive disorder using DSM-IV-TR criteria.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive either Brintellix 5, 10, 15, or 20 mg orally once daily or placebo. Patients who were randomized to 15 or 20 mg/day were titrated from 10 mg/day. The Montgomery-Asberg Depression Rating Scale (MADRS) was used for efficacy in 4 of the trials, while the Hamilton Depression Scale (HAMD-24) was used in 1 trial.
RESULTS	Baseline MADRS scores ranged from 31.2 +/- 3.4 to 34.1 +/- 2.6 across all 4 studies in which the MADRS was used. Brintellix significantly improved the total score of the MADRS in at least 1 group for each study, with a least-squares (LS) mean change from baseline ranging from -14.4 +/- 0.9 to -20.4 +/- 1 in the Brintellix groups compared with -10.8 +/- 0.8 to -14.5 +/- 1 in the placebo groups. In the study that used HAMD-24 total scores, the mean baseline score ranged from 32.2 +/- 5 to 33.1 +/- 4.8. The LS mean change from baseline ranged from -15.4 +/- 0.7 to -16.2 +/- 0.8 in the Brintellix groups compared with -11.3 +/- 0.7 in the placebo group. Higher doses (up to 20 mg/day) were associated with better treatment effects, while the 5 mg dose failed to demonstrate efficacy in 2 studies. In a subgroup analysis, there were no differences in clinical response based on age, gender, or race. Improvements in efficacy measures were generally seen at 2 weeks, with full antidepressant effects demonstrated at week 4 or later.
SAFETY	Not specified.

MAJOR DEPRESSIVE DISORDER - GERIATRIC PATIENTS – Study 2

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 6 to 8-week study (n=300).
INCLUSION CRITERIA	Geriatric patients, 64 to 88 years of age, with at least 1 previous major depressive disorder episode before age 60 years and without comorbid cognitive impairment based on a Mini Mental State Examination score of < 24.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive either Brintellix 5 mg orally once daily (n=155; mean baseline HAMD-24 score, 29.2 +/- 5) or placebo (n=145; mean baseline HAMD-24 score, 29.4 +/- 5.1).
RESULTS	The LS mean change from baseline on the HAMD-24 was -13.7 +/- 0.7 in the Brintellix group compared with -10.3 +/- 0.8 in the placebo group (treatment difference -3.3; 95% CI, -5.3 to -1.3).
SAFETY	Not specified.

MAJOR DEPRESSIVE DISORDER – MAINTENANCE – Study 3

STUDY DESIGN	Randomized, open-label, placebo-controlled, 24 to 64-week study (n=396).
INCLUSION CRITERIA	Adults with major depressive disorder by DSM-IV-TR criteria who achieved remission with vortioxetine treatment (MADRS total score of <= 10 at weeks 10 and 12).
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	In an initial 12-week treatment phase, patients with major depressive disorder received open-label oral Brintellix 5 or 10 mg once daily (n=639). Patients who achieved remission (MADRS total score of <= 10 at weeks 10 and 12; n=396) entered the continuation phase and were either randomized to a fixed dose of Brintellix, to continue at the final dose they responded to during the initial phase (75% on 10 mg/day), or to placebo for 24 to 64 weeks.
RESULTS	Approximately 61% of the randomized patients maintained remission for at least 4 weeks (since week 8), and 15% for at least 8 weeks (since week 4). Recurrence of depressive episodes was defined as a MADRS total score of >= 22 or lack of efficacy as judged by the investigator. Patients treated with Brintellix experienced a significantly longer time until recurrence than patients in the placebo arm.
SAFETY	Not specified.

Contraindications[1]

- Concomitant use with an MAOI within 14 days of discontinuing an MAOI used to treat psychiatric disorders or MAOI use within 21 days after Brintellix discontinuation, including linezolid or IV methylene blue; increased risk of serotonin syndrome
- Hypersensitivity to Brintellix or any component of the product

Warnings and Precautions[1]

- Suicidal ideation and behavior, worsening depression, or unusual changes in behavior may occur; increased risk in children, adolescents, and young adults; monitor all patients, especially during the first few months of therapy or with dose changes; discontinuation may be required.
- Bipolar disorder, history or family history; increased risk of precipitation of a mixed/manic episode with antidepressant treatment only.
- Bleeding events (eg, life-threatening hemorrhages, gastrointestinal bleeding, ecchymosis, hematoma, epistaxis, petechiae) may occur; increased risk with concomitant use of drugs that affect coagulation or bleeding (eg, NSAIDs, aspirin, warfarin).
- Hepatic impairment, severe; use not recommended.
- Hyponatremia and/or syndrome of inappropriate antidiuretic hormone secretion has been reported; increased risk in elderly and with volume-depletion or concurrent diuretic therapy; discontinue with symptomatic hyponatremia.
- Mania or hypomania, history or family history; risk of activation of mania/hypomania.
- Serotonin syndrome, potentially life-threatening, has been reported with serotonergic antidepressants; increased risk with concomitant use of serotonergic drugs (eg, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, St John's Wort) and drugs that impair metabolism of serotonin (eg, MAOIs, including methylene blue IV and

linezolid); monitoring recommended, especially at treatment initiation and with dose increases; if suspected, discontinue use and institute supportive therapy.

Adverse Effects[1]

Most common, >= 2%	Brintellix 10 mg/day (n=699)	Brintellix 20 mg/day (n=455)	Placebo (n=1621)
▪ Nausea	26%	32%	9%
▪ Diarrhea	7%	7%	6%
▪ Dry mouth	7%	8%	6%
▪ Dizziness	6%	9%	6%
▪ Constipation	5%	6%	3%
▪ Vomiting	5%	6%	1%
▪ Sexual dysfunction	5%	7%	2%
▪ Flatulence	3%	1%	1%
▪ Pruritus	2%	3%	1%
▪ Abnormal dreams	< 1%	3%	1%

Drug Interactions[1]

- Aspirin
- CYP inducers, strong: carbamazepine, phenytoin, rifampin
- CYP2D6 inhibitors, strong: bupropion, fluoxetine, paroxetine, quinidine
- MAOIs
- NSAIDs
- Serotonergic drugs: buspirone, tramadol, triptans, tryptophan
- Warfarin

Dosage and Administration[1]

The recommended dose is 10 mg orally once daily, increasing to 20 mg daily as tolerated. Dosage adjustments are necessary for CYP2D6 poor metabolizers or when used with concomitant strong CYP2D6 inhibitors or strong CYP inducers.

Cost

The cost per tablet of Brintellix, regardless of strength, is $7.27 each. WholesaleAcquisitionCost

Conclusion

Brintellix is a serotonergic antidepressant indicated for the treatment of major depressive disorder. It was evaluated in 6 double-blind, randomized, placebo-controlled trials, including one with elderly patients, and as continued maintenance treatment in an open-label, placebo-controlled clinical trial. Brintellix demonstrated efficacy compared with placebo in each trial, but has not been evaluated in comparison with other antidepressant agents. Brintellix was well-tolerated, with nausea as the most common adverse event.

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Recommendation

The Division recommends adding this drug to the current psychotropic polypharmacy clinical edit.

References

1. Product Information: Brintellix™, vortioxetine hydrobromide tablets. Takeda Pharmaceuticals America, Deerfield, IL, 09/2013.

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