Drug Monograph

Drug/Drug Class:	**Rexulti™ (brexpiprazole) tablet / Atypical Antipsychotics**
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:	Rexulti™ tablets are available in 6 strengths. It is available as a 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg of brexpiprazole respectively. Manufacturer: Otsuka America Pharmaceutical, Inc., Rockville, MD 20850
Summary of Findings:	Rexulti™ was evaluated in 4 randomized, double-blind, placebo-controlled, 6-week clinical trials that assessed its efficacy in adults. As adjunctive treatment in patients with MDD (N=627), an oral dosage of 3 mg daily, but not 1 mg daily, was effective at improving Montgomery- Asberg Depression Rating Scale (MADRS) scores compared with placebo. A dosage of 2 mg daily also demonstrated efficacy in MDD in a study of 353 patients. In patients with schizophrenia (N=623), Rexulti™ 2 mg and 4 mg significantly reduced the Positive and Negative Syndrome Scale (PANSS) scores from baseline compared with placebo; however, a second, similar trial (N=657) demonstrated only 4 mg daily produced significant improvements in the PANSS score compared with placebo.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Non-Preferred Agent

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[4]

Schizophrenia is a chronic, severe, and disabling brain disorder affecting about one percent of Americans. Typically, symptoms are first seen in adults younger than 30 years of age and include hearing voices; believing other people are reading their minds or controlling their thoughts; and being suspicious or withdrawn.

MDD, commonly referred to as depression, is also a severe and disabling brain disorder characterized by mood changes and other symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy once-pleasurable activities. Episodes of depression often recur throughout a person's lifetime, although some may experience a single occurrence. Other signs and symptoms of MDD include loss of interest in usual activities; significant change in weight or appetite; insomnia or excessive sleeping (hypersomnia); restlessness/pacing (psychomotor agitation); increased fatigue; feelings of guilt or worthlessness; slowed thinking or impaired concentration; and suicide attempts or thoughts of suicide. Not all people with MDD experience the same symptoms.

Dosage Form(s) [1]

Rexulti™ tablets are available in 6 strengths. It is available as a 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg of brexpiprazole respectively.

Manufacturer [1]

Otsuka America Pharmaceutical, Inc., Rockville, MD 20850

Indication(s) [1]

Rexulti™ is indicated for adjunctive treatment of major depressive disorder (MDD) and as treatment of schizophrenia in adults.

Clinical Efficacy [1,2,3] (mechanism of action/pharmacology, comparative efficacy)

Rexulti™ is an atypical antipsychotic. While its mechanism of action is unknown, it may be due to its activity as a partial agonist at D2 and 5-HT1A receptors and as an antagonist at 5-HT2A receptors.

Pharmacokinetics:

	Rexulti™
Volume of distribution	1.56 L/kg
Metabolism	Liver, via CYP2D6 and CYP3A4 to DM-3411 (inactive)

Excretion	Feces, 46% (14%, unchanged drug) Urine, 25% (<1%, unchanged drug)
Half-life	91 hours
Protein binding	> 99%, primarily to albumin and alpha-1-acid glycoprotein

MAJOR DEPRESSIVE DISORDER – ADJUNCTIVE THERAPY

Rexulti™ 3 mg daily, but not 1 mg daily, effectively improved depression scores compared with placebo in patients with MDD when added to their antidepressant therapy.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 6-week study (N=627).
INCLUSION CRITERIA	Adult patients with MDD (DSM-IV-TR criteria), with an inadequate response to 1 to 3 courses of prior therapy for the current episode, and who had an inadequate response of prospective antidepressant therapy over 8 weeks.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive Rexulti™ 1 mg or 3 mg orally once daily or placebo.
RESULTS	At week 6, Rexulti™ 3 mg significantly improved the MADRS score from baseline (-8.3 points) compared with placebo (-6.3 points), but Rexulti™ 1 mg did not (-7.6 points).
SAFETY	Not specified.

SCHIZOPRENIA

Treatment with Rexulti™ at dosages of 2 and 4 mg daily was effective compared with placebo in patients with an acute schizophrenic exacerbation.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 6-week phase 3 study (N=623).
INCLUSION CRITERIA	Adults (18 to 65 years) with schizophrenia (DSM-IV-TR criteria) experiencing an acute schizophrenic exacerbation, and who would benefit from treatment while hospitalized or with continued hospitalization.
EXCLUSION CRITERIA	Patients with a first episode of schizophrenia, a DSM-IV-TR axis 1 diagnosis other than schizophrenia, tardive dyskinesia, or substance abuse.

TREATMENT REGIMEN	Patients were randomized to receive Rexulti™ 0.25 mg, 2 mg, or 4 mg orally once daily or placebo.
RESULTS	At week 6, Rexulti™ 2 mg and 4 mg significantly reduced the PANSS score from baseline (-20.73 and -19.65 points, respectively) compared with placebo (-12.01 points). The response rate, defined as an improvement of at least 30% in the PANSS score, was 47.8% with 2 mg/day, 46.1% with 4 mg/day, and 30.3% with placebo. The mean change from baseline in the total Clinical Global Impressions (CGI) severity score was also significantly improved with Rexulti™ 2 mg and 4 mg compared with placebo.
SAFETY	The rates of adverse effects and discontinuation due to adverse effects were lower in the Rexulti™ groups compared with placebo.

Contraindications [(1)]

- Hypersensitivity to brexpiprazole or any component of the product

Warnings and Precautions [(1)]

- Elderly patients with dementia-related psychosis (unapproved use) are at an increased risk of death.
- Suicidality, unusual changes in behavior, and worsening of depression may occur; increased risk in children, adolescents, and young adults (ages 18 to 24 years); monitoring recommended and discontinuation may be necessary.
- Orthostatic hypotension has been reported; monitoring and dose reductions recommended.
- Concomitant use of CYP2D6 inhibitors; dose adjustment recommended.
- Concomitant use of CYP3A4 inhibitors; dose adjustment recommended.
- Concomitant use of strong CYP3A4 inducers; dose adjustment recommended.
- Hyperglycemia, possibly associated with ketoacidosis, hyperosmolar coma, and death, has been reported; monitoring recommended.
- Worsening of glucose control may occur in patients with diabetes mellitus; monitoring recommended and discontinuation may be required.
- Lipid alterations have been reported; monitoring recommended.
- Weight gain has been reported; monitoring recommended.
- Body temperature dysregulation may occur.
- Leukopenia, neutropenia, and agranulocytosis may occur; monitoring recommended and discontinuation may be required.
- Hepatic impairment, moderate to severe; dose reduction recommended.
- Neuroleptic Malignant Syndrome may occur and may be fatal; monitoring may be warranted and immediate discontinuation is required.
- Elderly patients with dementia-related psychosis (unapproved use) are at increased risk of cerebrovascular accidents and transient ischemic attacks, including fatalities.
- Tardive dyskinesia may occur; increased risk in women and elderly patients; monitoring recommended and discontinuation may be warranted.

- Use caution in patients with a history of seizures or a condition that may lower the seizure threshold.
- Poor CYP2D6 metabolizers; dose adjustments recommended.
- Renal impairment, moderate to severe, or ESRD; dose reduction recommended.
- Esophageal motility and aspiration may occur; use caution in patients at risk for aspiration pneumonia.

Adverse Effects [(1)]

Major Depressive Disorder

Most Common, ≥ 2%	Rexulti™ (n=643)	Placebo (n=411)
Akathisia	9%	2%
Headache	7%	6%
Weight increased	7%	2%
Somnolence	5%	0.5%
Nasopharyngitis	4%	2%
Tremor	4%	2%
Anxiety	3%	1%
Dizziness	3%	1%
Fatigue	3%	2%
Increased appetite	3%	2%
Restlessness	3%	0%
Blood cortisol decreased	2%	1%
Constipation	2%	1%

Schizophrenia

Most Common, ≥ 2%	Rexulti™ (n=852)	Placebo (n=368)
Akathisia	6%	5%
Weight increased	4%	2%
Diarrhea	3%	2%
Dyspepsia	3%	2%
Tremor	3%	1%

Blood creatine phosphokinase increased	2%	1%
Sedation	2%	1%

Drug Interactions [1]

- CYP2D6 inhibitors: quinidine, paroxetine, fluoxetine
- CYP3A4 inducers, strong: rifampin, St. John's wort
- CYP3A4 inhibitors: ketoconazole, itraconazole, clarithromycin

Dosage and Administration [1]

Adjunctive treatment for MDD: Initially, 0.5 mg or 1 mg orally once daily; titrate at weekly intervals based on clinical response and tolerability to 1 mg once daily, then to target dose of 2 mg once daily; maximum dose is 3 mg/day. Treatment of schizophrenia: Initially, 1 mg orally once daily for 4 days; based on clinical response and tolerability, titrate to 2 mg once daily for 3 days, then to 4 mg once daily; target dose is 2 mg to 4 mg once daily; maximum dose is 4 mg/day. Dosage adjustments are recommended for hepatic impairment, renal impairment, CYP2D6 poor metabolizers, and in patients receiving concomitant CYP2D6 inhibitors, CYP3A4 inhibitors, or strong CYP3A4 inducers.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ MONTH
Brexpiprazole	Rexulti	Otsuka	0.25 mg tablets	1 tablet daily	$865.50
			0.5 mg tablets	1 tablet daily	$865.50
			1 mg tablets	1 tablet daily	$865.50
			2 mg tablets	1 tablet daily	$865.50
			3 mg tablets	1 tablet daily	$865.50
			4 mg tablets	1 tablet daily	$865.50
Aripiprazole	Abilify	Bristol-Myers Squibb	2 mg tablets	1 tablet daily	$891.90
			5 mg tablets	1 tablet daily	$891.90
			10 mg tablets	1 tablet daily	$891.90
			15 mg tablets	1 tablet daily	$891.90
			20 mg tablets	1 tablet daily	$1,261.20
			30 mg tablets	1 tablet daily	$1,261.20

* Wholesale Acquisition Cost

Conclusion

Rexulti™ is an oral atypical antipsychotic indicated in adults both as adjunct therapy for major depressive disorder and for the treatment of schizophrenia. In two, 6-week randomized trials in MDD patients with an inadequate response to prior antidepressant therapy and an inadequate response to ongoing therapy (N=980), Rexulti™ 2 mg and 3 mg daily significantly improved the mean MADRS score compared with placebo. In two, 6-week randomized trials in patients with schizophrenia (N=1280), Rexulti™ 4 mg significantly reduced the mean total PANSS score compared with placebo, while Rexulti™ 2 mg produced conflicting results. Rexulti™ is not indicated for the treatment of elderly patients with dementia-related psychosis because of increased risk of death. Rexulti™ is generally well-tolerated, with the most common adverse effects being increased weight and akathisia. Clinical trials comparing Rexulti™ with other atypical antipsychotics are lacking.

Recommendation

The Division recommends adding this drug to the current atypical antipsychotic clinical edit.

References

1. Product Information: Rexulti™, brexpiprazole tablets. Otsuka America Pharmaceutical Inc. Rockville, MD, 07/2015
2. Correll CU, Skuban A, Ouyang J et al: Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: A 6-week randomized, double-blind, placebo-controlled trial. Am J Psychiatry 2015; 172(9):870-880.
3. Kane JM, Skuban A, Ouyang J et al: A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res 2015; 164(1-3):127-135.
4. FDA Approves new drug to treat schizophrenia and as an add on to an antidepressant to treat major depressive disorder. Retrieved 11/10/15 from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm454647.htm

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