BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

REXULTI® (brexpiprazole) Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Rexulti (brexpiprazole) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist

2. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Adjunctive therapy used with an antidepressant in an individual is 18 years of age or older with Major Depressive Disorder (MDD)
    b. Individual who is 13 years of age or older with Schizophrenia
    c. Individual who is 18 years of age or older for treatment of agitation associated with dementia due to Alzheimer's disease diagnosed according to National Institute of Neurological and

Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria

3. **Additional criteria for agitation associated with dementia in Alzheimer's disease**, **ALL** of the following:
    a. Individual does **not** have dementia-related psychosis without agitation due to Alzheimer's disease
    b. Has a previous MRI or CT scan of the brain, that was performed after the onset of symptoms of dementia, with findings consistent with a diagnosis of Alzheimer's disease
    c. Has a Mini-Mental State Examination (MMSE) score of ≥ 5 and ≤ 22
    d. Has a total score of ≥ 4 by the agitation/aggression item of the Neuropsychiatric Inventory-Nursing Home (NPI-NH)
    e. Exhibits sufficient agitation behaviors to warrant use of pharmacotherapy, after excluding other factors

4. Will not be used on an as needed treatment for agitation associated with dementia due to Alzheimer's disease

5. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Fasting plasma glucose
    b. Lipid profile
    c. Weight

6. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. **ONE** the following:
    a. **For Major Depressive Disorder**: Failure (after 6-weeks at maximally tolerated dose), contraindication per FDA label, intolerance, or is not a candidate for a total of **TWO** medications from the following categories: (must not be from the same category)
        i. Selective Serotonin Reuptake Inhibitor (e.g., citalopram, escitalopram, fluoxetine, paroxetine, paroxetine extended release, sertraline)
        ii. Serotonin-Norepinephrine Reuptake Inhibitor (e.g., duloxetine delayed release, venlafaxine, venlafaxine extended release)
        iii. Bupropion or mirtazapine
    b. **For Schizophrenia**: Failure (after 6-weeks at maximally tolerated dose), contraindication per FDA label, intolerance, or is not a candidate for **TWO** of the following:
        i. Aripiprazole (brand or generic)
        ii. Lurasidone (brand or generic)
        iii. Olanzapine (brand or generic)
        iv. Quetiapine (brand or generic)
        v. Quetiapine XR (brand or generic)
    c. **For agitation associated with dementia in Alzheimer's Disease**: Failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** of the following:
        i. Olanzapine
        ii. Quetiapine

8. Individual does not have a recent history of myocardial infarction or unstable cardiovascular disease

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Rexulti (brexpiprazole) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist

2. Individual's condition has responded while on therapy with response defined as the following:
    a. **For Major Depressive Disorder:**
        i. Documented evidence of efficacy, disease stability and/or improvement
        ii. Improved mood, behavior, interest in daily activities, sleep, energy, sense of worthiness, no thoughts of suicide and no attempts, no aggression or violent behavior, no hospitalizations
    b. **For schizophrenia:**
        i. Documented evidence of efficacy, disease stability and/or improvement
        ii. Fewer hallucinations, delusions, disorganized thoughts and behaviors, improved affect, improved socialization, improved energy, fewer to no hospitalizations over baseline
    c. **For Alzheimer's Disease:**
        i. Improvement in aggressive behavior (e.g., screaming, throwing things, cursing/verbal aggression, kicking, pushing scratching, hurting self or others)
        ii. Improvement in physically non-aggressive behavior (e.g., repetitive mannerisms, general restlessness, pacing)
        iii. Improvement in verbally agitated behavior (e.g., complaining, repetitive questions, constant requests for attention)

3. **Additional criteria for Alzheimer's Disease**: Individual does **NOT** have dementia-related psychosis without agitation due to Alzheimer's disease

4. Individual has been adherent with the medication **AND** if used for Major Depressive Disorder, is adherent with an antidepressant

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Absolute neutrophil count is < 1,000/mm^3
    b. Neuroleptic malignant syndrome
    c. Persistent or worsening depression
    d. Emergent suicidal thoughts or behaviors
    e. Pathologic gambling and other compulsive behaviors

f. Tardive dyskinesia (TD), unless provider indicates continued need for Rexulti therapy and may or may not be accompanied by treatment of TD

7. Individual does not have a recent history of myocardial infarction or unstable cardiovascular disease

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Rexulti (brexpiprazole) is indicated as adjunctive treatment to antidepressant medications for individuals 18 years of age or older with major depressive disorder (MDD); it is indicated for the treatment of schizophrenia in individuals 13 years of age or older; and it is indicated for the treatment of agitation associated with dementia due to Alzheimer's disease in individuals 18 years of age or older. It is not indicated for "as needed use" for the treatment of agitation associated with dementia due to Alzheimer's disease.

The mechanism of action of brexpiprazole in the treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors. Brexpiprazole is considered an atypical or second-generation antipsychotic that acts primarily to modulate serotonin and dopamine activity. It is structurally similar to aripiprazole (Abilify), another second-generation antipsychotic. Numerous generic formulations are available for the treatment of schizophrenia and major depressive disorder.

Antipsychotics are recognized as being effective for the treatment of schizophrenia. They are categorized as first-generation agents (such as haloperidol, loxapine, and others) and as second-generation agents (such as aripiprazole, clozapine, olanzapine, and others). Second generation agents are also referred to as atypical agents.

Atypical second-generation antipsychotics are preferred over first-generation (typical) antipsychotics due to the lower incidence of extrapyramidal side effects and tardive dyskinesia. Second generation agents have variable effects on weight gain, increase in blood glucose and diabetes, increase in lipids, movement disorder, and effect on QTc prolongation.

Antipsychotic drug selection may be determined by several factors such as previous treatment response, adverse event profile of potential agents, patient preference, route of administration, comorbid medical conditions, and potential for drug-drug interactions. With the exception of clozapine, there is no reliable evidence that one atypical antipsychotic is more effective than another. Because olanzapine is associated with significant weight gain and metabolic adverse effects, leading guidelines state that it should not be used as a first-line agent for first-episode patients, but should be considered for patients who fail treatment with a first-line agent.

Switching antipsychotics can be helpful when a poor response is related to side effects. It is less clear that switching antipsychotics is beneficial when the initial medication lacked effectiveness. Most studies have shown that poor responders to one antipsychotic are likely to be poor responders to another antipsychotic except when the second agent is clozapine.

Adding a second antipsychotic medication has not been proven efficacious in randomized trials. For patients with psychotic symptoms that do not respond to two trials of antipsychotic monotherapy, a trial of clozapine is strongly recommended before combining two antipsychotics.

Long-acting injectable (LAI) antipsychotic medication may be useful for patients with schizophrenia when non-adherence to oral antipsychotics leads to frequent relapse.

Major depressive disorder (MDD), also known as unipolar depressive disorder, is diagnosed in a patient who has suffered at least one major depressive episode and has no history of mania or hypomania. A major depressive episode is a period lasting at least two weeks, with five or more of the following symptoms: depressed mood, anhedonia, insomnia, or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, thoughts of worthlessness or guilt, and recurrent thoughts about death or suicide. At least one of the symptoms must be depressed mood or anhedonia.

Treatment resistant depression refers to major depressive episodes that do not respond satisfactorily to at least two trials of antidepressant monotherapy; however, the definition has not been standardized. Treatment refractory depression refers to unipolar major depressive episodes that do not respond satisfactorily to numerous sequential treatment regimens; however, the definition has not been standardized. There is no clear delineation between treatment resistant and treatment refractory depression.

Unipolar major depression should be treated with medication for 6-12 weeks before deciding whether the antidepressant has sufficiently relieved symptoms. However, for patients who show little improvement (reduction of baseline symptoms ≤ 25%) after 4-6 weeks, it is reasonable to administer next-step treatment.

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), mirtazapine and bupropion, are recommended by guidelines as first line treatment for patients with MDD. Efficacy among the various agents is similar and drug selection is guided by the same factors as those mentioned above for antipsychotics for schizophrenia.

The standard of care for MDD patients with an inadequate response to monotherapy may include: a) optimizing the antidepressant dose for patients who show minimal or no response, b) transition to another antidepressant, c) the current antidepressant may be augmented with a second antidepressant from a different class, lithium carbonate, thyroid hormone or an atypical antipsychotic, and d) electroconvulsive therapy for treatment resistant patients with severe unipolar major depression or severe unipolar major depression with psychotic features (delusions or hallucinations).

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

PHARMACY COVERAGE GUIDELINE

REXULTI® (brexpiprazole)
Generic Equivalent (if available)

Atypical (second generation) antipsychotics:

Generic agents*	Brand agents*
- aripiprazole (generic for Abilify) - clozapine (generic for Clozaril) - olanzapine (generic for Zyprexa) - palperidone ER (generic for Invega) - quetiapine (generic for Seroquel) - quetiapine XR (generic Seroquel XR) - risperidone (generic for Risperdal) - ziprasidone (generic for Geodon)	- aripiprazole lauroxil (Aristada) injection - asenapine (Saphris) - brexpiprazole (Rexulti) - cariprazine (Vraylar) - iloperidone (Fanapt) - lumateperone (Caplyta) - lurasidone (Latuda)

Informational purposes only, listing does not imply formulary status or whether or not precertification is required

Alzheimer's Disease:
National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) NINCDS-ADRDA Criteria for Alzheimer's Disease - MDCalc
*Required criteria for **Definite** AD*:

1. Histopathologic evidence obtained from a biopsy or autopsy **plus**
2. All criteria for ***Probable*** AD (1-6 below).

*Criteria for **Probable** AD* (must have all 6)*:

1. Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests
2. Deficits in ≥ 2 areas of cognition
3. Progressive worsening of memory and other cognitive functions
4. No disturbance of consciousness
5. Onset at age > 40 to < 90 years
6. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

*The diagnosis of **Probable** AD is supported by the following:

a) Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia)
b) Impaired activities of daily living and altered patterns of behavior
c) Family history of similar disorders, particularly if confirmed neuropathologically
d) Lab results:
   i. Normal lumbar puncture
   ii. Normal pattern or nonspecific changes in EEG (e.g., increased slow-wave activity)
   iii. Cerebral atrophy on CT with progression documented by serial observation.

Features that make **Probable** AD diagnosis **uncertain or unlikely**:

a) Sudden, apoplectic onset
b) Focal neurologic findings (e.g., hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness)
c) Seizures or gait disturbances at onset or very early in the course of the illness.

If neither of the above is fulfilled then:

*Criteria for **Possible** AD (must have all 3)*:

1. Dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and presence of variations in onset, in presentation, or in clinical course
2. Presence of a second systemic or brain disorder sufficient to produce dementia but is not considered to be the cause of dementia
3. A single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause

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Resources:

Rexulti (brexpiprazole) product information, revised by Otsuka America Pharmaceutical, Inc. 05-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed March 14, 2024.

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