PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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REXULTI® (brexpiprazole)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

REXULTI® (brexpiprazole)

Criteria:

- **Criteria for initial therapy:** Rexulti (brexpiprazole) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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

  2. A confirmed diagnosis of **ONE** of the following:
     a. Individual is 18 years of age or older with Major Depressive Disorder (MDD), to be used as adjunctive therapy with an antidepressant(s)
     b. Individual is 13 years of age or older with Schizophrenia

  3. Individual does not have dementia-related psychosis

  4. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Fasting plasma glucose
     b. Lipid profile
     c. Weight

  5. **ONE** of the following:
     a. **For Major Depressive Disorder**: Failure (after 6-weeks at maximally tolerated dose), contraindication per FDA label or intolerance to **THREE** medications in at least **TWO** of the following categories:
        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 or intolerance to **THREE** of the following:
        i. Aripiprazole (brand or generic)
        ii. Olanzapine (brand or generic)
        iii. Paliperidone (brand or generic)
        iv. Quetiapine (brand or generic)
        v. Quetiapine XR (brand or generic)
        vi. Risperidone (brand or generic)

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

  Initial approval duration: 6 months

REXULTI® (brexpiprazole)

- **Criteria for continuation of coverage (renewal request):** Rexulti (brexpiprazole) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  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 responded while on therapy
     a. Response is defined as:
        i. For Major Depressive Disorder:
           1. Documented evidence of efficacy, disease stability and/or improvement
           2. 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
        ii. For schizophrenia:
           1. Documented evidence of efficacy, disease stability and/or improvement
           2. Fewer hallucinations, delusions, disorganized thoughts and behaviors, improved affect, improved socialization, improved energy, fewer to no hospitalizations over baseline

  3. Individual has been adherent with the medication **AND** if used for Major Depressive Disorder, is adherent with antidepressant(s)

  4. Individual has not developed any or other significant adverse drug effects that may exclude continued use
     a. Significant adverse effect such as:
        i. Absolute neutrophil count is < 1,000/mm^3
        ii. Neuroleptic malignant syndrome
        iii. Persistent or worsening depression
        iv. Emergent suicidal thoughts or behaviors
        v. Pathologic gambling and other compulsive behaviors
        vi. Tardive dyskinesia (TD), unless provider indicates continued need for Rexulti therapy and may or may not be accompanied by treatment of TD

  5. There are no significant interacting drugs

  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**

REXULTI® (brexpiprazole)

Description:

Rexulti (brexpiprazole) is indicated as adjunctive treatment to antidepressant medications for adults with major depressive disorder (MDD) and for the treatment of adults with schizophrenia. It is not approved for the treatment of patients with dementia-related psychosis.

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:

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

REXULTI® (brexpiprazole)

Resources:

Rexulti (brexpiprazole) product information, revised by Otsuka America Pharmaceutical, Inc. 12-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 03, 2022.

Rush AJ. Unipolar major depression in adults: Choosing initial treatment. In: UpToDate, Roy-Byrne PP, Solomon D (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated November 18, 2020. Accessed May 03, 2022.

Thase M, Connolly KR. Unipolar depression in adults: Management of highly resistant (refractory) depression. In: UpToDate, Roy-Byrne PP, Solomon D (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated August 31, 2021. Accessed May 03, 2022.

Kane J, Rubio JM, Kishimoto T, Correll CU. Evaluation and management of treatment-resistant schizophrenia. In: UpToDate, Marder S, Friedman M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated March 09, 2021. Accessed May 03, 2022.

Siris SG, Braga RJ. Depression in schizophrenia. In: UpToDate, Marder S, Friedman M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated December 28, 2020. Accessed May 04, 2022.