BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 11/19/15**
SECTION: DRUGS	**LAST REVIEW DATE: 11/16/17**
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	ARCHIVE DATE:

REXULTI® (brexpiprazole) oral tablet

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) oral tablet (cont.)

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.

Schizophrenia

- 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
    - Switching antipsychotics is less clearly 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

REXULTI® (brexpiprazole) oral tablet (cont.)

- 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)

- 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
  - 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, and 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 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:
  - Optimizing the antidepressant dose for patients who show minimal or no response
  - Transition to another antidepressant
  - The current antidepressant may be augmented with a second antidepressant from a different class, lithium carbonate, thyroid hormone or an atypical antipsychotic

REXULTI® (brexpiprazole) oral tablet (cont.)

- 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) - lurasidone (Latuda) - pimavanserin (Nuplazid)

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

Rexulti (brexpiprazole)

Medication class:
Second generation (atypical) antipsychotic

FDA-approved indication(s):
- Adjunctive treatment of major depressive disorder (MDD)
- Treatment of schizophrenia

Recommended Dose:
- MDD:
  - Recommended starting dosage is 0.5 mg or 1 mg once daily, titrate to 1 mg once daily, then up to the target dosage of 2 mg once daily. Dosage increases should occur at weekly intervals
- Schizophrenia:
  - Recommended starting dosage is 1 mg once daily on days 1-4, the target dosage is 2-4 mg once daily, titrate to 2 mg once daily on days 5-7, then 4 mg once daily on day 8

Maximum dosage
- MDD:
  - 3 mg once daily
  - 2 mg once daily if have moderate to severe hepatic impairment (Child-Pugh Class > B, score $\geq$ 7)
  - 2 mg once daily if have moderate, severe, or ESRD (CrCl < 60 mL/min)

REXULTI® (brexpiprazole) oral tablet (cont.)

- Schizophrenia:
  - 4 mg once daily
  - 3 mg once daily if have moderate to severe hepatic impairment (Child-Pugh Class > B, score ≥ 7)
  - 3 mg once daily if have moderate, severe, or ESRD (CrCl < 60 mL/min)

Available Dosage Forms:
- 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets

Warnings and Precautions:
- Rexulti is not approved for treatment of patients with dementia-related psychosis
- Discontinue if neuroleptic malignant syndrome occurs or is suspected
- Consider discontinuing if tardive dyskinesia occurs
- Consider discontinuing if a clinically significant drop in WBC occurs in the absence of other known cause
- Discontinue if absolute neutrophil count is < 1,000/mm^3
- Consider discontinuing if depression is persistently worse or if the patient is experiencing emergence of suicidal thoughts or behaviors
- It is not approved for: Bipolar disorder, Autistic disorder, Agitation associated with Alzheimer's disease, Post-traumatic Stress Disorder, Personality disorder, Dementia, or Attention Deficit Hyperactivity disorder
- Metabolism of Rexulti is through CYP3A4 and CYP2D6, drug interactions are possible
- Poor CYP2D6 metabolizer – give half the usual dose of Rexulti
- Poor CYP2D6 metabolizer using strong/moderate CYP3A4 inhibitor – give quarter the usual Rexulti dose
- Using strong CYP2D6 inhibitor – give half the usual dose of Rexulti, if Rexulti is being used for MDD a dose adjustment is not needed
- Using strong CYP3A4 inhibitor – give half the usual dose of Rexulti
- Using strong/moderate CYP3A4 inhibitor and strong/moderate CYP2D6 inhibitor – give one-quarter the usual Rexulti dose
- Using with a CYP3A4 inducer – increase Rexulti dose

REXULTI® (brexpiprazole) oral tablet (cont.)

Precertification:

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

  1. Individual is 18 years of age or older

  2. A confirmed diagnosis of **ONE** of the following:
     - Major Depressive Disorder (MDD), as adjunctive therapy to an antidepressant
     - Schizophrenia

  3. Individual has failure, contraindication or intolerance to following preferred step therapy agents:
     - Preferred step therapy for MDD as adjunct therapy to an antidepressant, unable to use **THREE** of the following:
       - Aripiprazole (generic)
       - Olanzapine – Fluoxetine (generic)
       - Quetiapine XR (generic)
       - Risperidone (generic)
       - Ziprasidone (generic)
     - Preferred step therapy for schizophrenia, unable to use **THREE** of the following:
       - Aripiprazole (generic)
       - Asenapine (Saphris)
       - Clozapine (generic)
       - Iloperidone (Fanapt)
       - Lurasidone (Latuda)
       - Olanzapine (generic)
       - Paliperidone (generic)
       - Quetiapine (generic)
       - Quetiapine XR (generic)
       - Risperidone (generic)
       - Ziprasidone (generic)

  4. There are **NO** contraindications:
     - Contraindications include:
       - Known hypersensitivity to Rexulti or any of its components

  Initial approval duration: 6 months

REXULTI® (brexpiprazole) oral tablet (cont.)

- **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's condition responded while on therapy
    - Response is defined as:
        - For MDD:
            - 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
        - For schizophrenia:
            - Fewer hallucinations, delusions, disorganized thoughts and behaviors, improved affect, improved socialization, improved energy, fewer to no hospitalizations over baseline

2. Individual has been adherent with the medication **and** adherent with antidepressant

3. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Adverse effect such as:
        - Absolute neutrophil count is < 1,000/mm^3
        - Neuroleptic malignant syndrome
            - Signs and symptoms may include: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure
        - Tardive dyskinesia
            - Signs and symptoms may include: Involuntary abnormal movements of the face, tongue or other body parts
        - Persistent or worsening depression
        - Suicidal thoughts or behaviors

4. There are no significant interacting drugs

Renewal duration: 12 months

Resources:

Rexulti. Package Insert. Revised by manufacturer 07/2015. Accessed 08-14-2015.

Tundo A, de Filippis R, and Proiett L: Pharmacologic approaches to treatment resistant depression: Evidences and personal experiences. WJP 2015 Sept 22;5(3):330-341

Spielmans GI, Berman MI, Linardatos E, et al.: Adjunctive Atypical Antipsychotic Treatment for Major Depressive Disorder: A Meta-Analysis of Depression, Quality of Life, and Safety Outcomes. PLoS Med 2013 10(3): e1001403. doi:10.1371/journal.pmed.1001403

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Kato M and Chang CM: Augmentation Treatments with Second-generation Antipsychotics to Antidepressants in Treatment-resistant Depression. CNS Drugs 2013; 27 (Suppl 1):S11–S19

Wang SM, Han C, Lee SJ, et al.: Second Generation Antipsychotics in the Treatment of Major Depressive Disorder: An Update. Chonnam Med J 2016;52:159-172. https://doi.org/10.4068/cmj.2016.52.3.159

UpToDate: Unipolar major depression in adults: Choosing initial treatment. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/unipolar-major-depression-in-adults-choosing-initial-treatment?source=search_result&search=major%20depressive%20disorder&selectedTitle=1~150

UpToDate: Unipolar major depression in adults: Treatment of resistant depression. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/unipolar-depression-in-adults-treatment-of-resistant-depression?source=see_link

UpToDate: Unipolar major depression in adults: Management of highly resistant (refractory) depression. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/unipolar-depression-in-adults-management-of-highly-resistant-refractory-depression?source=see_link

UpToDate: Overview of prevention and treatment for pediatric depression. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-prevention-and-treatment-for-pediatric-depression?source=search_result&search=major%20depressive%20disorder&selectedTitle=3~150

UpToDate: Pharmacotherapy for schizophrenia: Acute and maintenance phase treatment. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/pharmacotherapy-for-schizophrenia-acute-and-maintenance-phase-treatment?source=search_result&search=schizophrenia&selectedTitle=2~150#H2758642

UpToDate: Schizophrenia in adults: Clinical manifestations, course, assessment, and diagnosis. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/schizophrenia-in-adults-clinical-manifestations-course-assessment-and-diagnosis?source=search_result&search=schizophrenia&selectedTitle=1~150

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.