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.

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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. 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 by medical guidelines as being effective for the treatment of schizophrenia. They are often categorized as first generation agents (such as haloperidol, lozapine, 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 antipsychotics are commonly preferred over first-generation (typical) antipsychotics due to the lower incidence of extrapyramidal side effects and tardive dyskinesia. The second generation agents have variable effects on weight gain, increase in blood glucose and diabetes, increase in lipids, movement disorder, and
REXULTI® (brexpiprazole) oral tablet (cont.)

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.

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 or the current antidepressant may be augmented with a second antidepressant from a different class, lithium carbonate, thyroid hormone or an atypical antipsychotic.

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.

**Definitions:**

**Atypical (second generation) antipsychotics:**

<table>
<thead>
<tr>
<th>Generic agents*</th>
<th>Brand agents*</th>
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</thead>
<tbody>
<tr>
<td>- aripiprazole (generic for Abilify)</td>
<td>- asenapine (Saphris)</td>
</tr>
<tr>
<td>- clozapine (generic for Clozaril)</td>
<td>- iloperidone (Fanapt)</td>
</tr>
<tr>
<td>- olanzapine (generic for Zyprexa)</td>
<td>- lurasidone (Latuda)</td>
</tr>
<tr>
<td>- paliperidone ER (generic for Invega)</td>
<td>- quetiapine XR (Seroquel XR)</td>
</tr>
<tr>
<td>- quetiapine (generic for Seroquel)</td>
<td></td>
</tr>
<tr>
<td>- risperidone (generic for Risperdal)</td>
<td></td>
</tr>
<tr>
<td>- ziprasidone (generic for Geodon)</td>
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</tr>
</tbody>
</table>

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

**Drug related events:**

**Ineffective / failure**

Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.
Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

*Allergic reaction / hypersensitivity* – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

*Intolerance* – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer's labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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](http://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.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Rexulti (brexpiprazole) requires completion of the specific request form in its entirety. 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 will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Rexulti is considered medically necessary when ALL of the following criteria are met:

  1. Individual is 18 years of age or older

  2. Medical record documentation of a confirmed diagnosis of ONE of the following:
     - Major Depressive Disorder (MDD), as adjunctive therapy to antidepressants
     - Schizophrenia

  3. Individual is unable to use the following preferred agents due to either ineffectiveness, intolerance, or contraindication:
     - For MDD as adjunct therapy to antidepressants, unable to use ALL of the following:
       - Aripiprazole (generic)
       - Olanzapine – Fluoxetine (generic)
       - Quetiapine XR (generic)
       - Risperidone (generic)
       - Ziprasidone (generic)
     - For schizophrenia, unable to use ALL of the following:
       - Aripiprazole (generic)
       - Asenapine (Saphris)
       - Clozapine (generic)
       - Iloperidone (Fanapt)
       - Lurasidone (Latuda)
       - Olanzapine (generic)
       - Paliperidone (generic)
       - Quetiapine (generic)
       - Risperidone (generic)
       - Ziprasidone (generic)

  4. Absence of ALL of the following contraindications:
     - Known hypersensitivity to Rexulti or any of its components
Rexulti® (brexpiprazole) oral tablet (cont.)

- Rexulti for all other indications not previously listed is considered **experimental or investigational** based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Bipolar disorder
- Autistic disorder
- Agitation associated with Alzheimer’s disease
- Post-traumatic Stress Disorder
- Personality disorder
- Dementia
- Attention Deficit Hyperactivity disorder

**Resources:**


**REXULTI® (brexpiprazole) oral tablet** (cont.)

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
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<tbody>
<tr>
<td>REXULTI is an atypical antipsychotic indicated for:</td>
<td>Administer REXULTI once daily with or without food</td>
</tr>
<tr>
<td>• Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD)</td>
<td></td>
</tr>
<tr>
<td>• Treatment of schizophrenia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th>Starting Dose</th>
<th>Recommended Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMD</td>
<td>0.5 mg/day or 1 mg/day</td>
<td>2 mg/day</td>
<td>3 mg/day</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1 mg/day</td>
<td>2 to 4 mg/day</td>
<td>4 mg/day</td>
</tr>
</tbody>
</table>

- Moderate to Severe Hepatic Impairment (Child-Pugh score ≥7): Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia
- Moderate, Severe or End-Stage Renal Impairment (CrCl < 60 mL/minute): Maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia
- Known CYP2D6 Poor Metabolizers: Reduce the usual dosage by half