Clinical Policy: Brexpiprazole (Rexulti)

Reference Number: CP.PMN.68
Effective Date: 11.05.15
Last Review Date: 02.18
Line of Business: Commercial, Health Insurance Marketplace, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Brexpiprazole (Rexulti®) is an atypical antipsychotic.

FDA Approved Indication(s)
Rexulti is indicated for the:
- Adjunctive treatment of major depressive disorder (MDD)
- Treatment of schizophrenia.

Policy/Criteria
Provider must submit documentation (including such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Rexulti is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Major Depressive Disorder (must meet all)**:**
1. Diagnosis of MDD;
2. Age ≥ 18 years;
3. Failure of THREE antidepressants (e.g., SSRI, SNRI, TCA, bupropion, mirtazapine, etc.) from at least TWO different classes at up to maximally indicated doses, each trialed for ≥ 4 weeks, unless contraindicated or clinically significant adverse effects are experienced;
4. Failure of ≥ 4 week trial of aripiprazole, used concurrently with an antidepressant, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Rexulti is prescribed concurrently with an antidepressant;
6. Dose does not exceed 3 mg per day (1 tablet/day).

Approval duration:
Medicaid/Health Insurance Marketplace – 12 months
Commercial – Length of Benefit

B. Schizophrenia (must meet all)**:**
1. Diagnosis of schizophrenia;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):

a. Failure of two of the following atypical antipsychotics: risperidone, quetiapine, olanzapine, or ziprasidone at up to maximally indicated doses, each trialed for ≥ 4 weeks, unless contraindicated or clinically significant adverse effects are experienced;
b. Member has diabetes mellitus or body mass index (BMI) > 30;

4. Failure of ≥ 4 week trial of aripiprazole at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 4 mg per day (1 tablet/day).

Approval duration:
Medicaid/Health Insurance Marketplace – 12 months
Commercial – Length of Benefit

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Documentation supports that member is currently receiving Rexulti for schizophrenia and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed (a or b):
   a. MDD: 3 mg per day (1 tablet per day);
   b. Schizophrenia: 4 mg per day (1 tablet per day).

Approval duration:
Medicaid/Health Insurance Marketplace – 12 months
Commercial – Length of Benefit

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies –

CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BMI: body mass index
CrCl: creatinine clearance
CYP: cytochrome P450
FDA: Food and Drug Administration
MDD: major depressive disorder
SNRI: serotonin-norepinephrine reuptake inhibitors
SSRI: selective serotonin reuptake inhibitors
TCA: tricyclic antidepressants

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
aripiprazole (Abilify®)	10-30 mg by mouth daily	30 mg/day
ziprasidone (Geodon®)	40-80 mg by mouth twice daily	160 mg/day
risperidone (Risperdal®)	1-4 mg by mouth daily to twice daily	16 mg/day
quetiapine (Seroquel®)	400-800 mg/day by mouth twice daily to three times daily in divided doses	800 mg/day
olanzapine (Zyprexa®)	10-20 mg by mouth daily	20 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: General Information

Rexulti has a black box warning for increased mortality in elderly patients with dementia-related psychosis; and suicidal thoughts and behaviors.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Rexulti is not approved for the treatment of patients with dementia-related psychosis.
- Antidepressants increase the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors.
- Safety and effectiveness of Rexulti have not been established in pediatric patients.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Adjunctive treatment of MDD	0.5 mg or 1 mg once daily, up to the target dosage of 2 mg once daily	3 mg/day

Indication	Dosing Regimen	Maximum Dose
Schizophrenia	1 mg once daily, up to target dosage of 2 mg to 4 mg once daily	4 mg/day

- *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 [creatinine clearance (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 cytochrome P450 (CYP) 2D6 Poor Metabolizers:* Reduce the usual dosage by half

VI. Product Availability

Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

VII. References

1. Rexulti Prescribing Information. Rockville, MD: Otsuka America Pharmaceutical, Inc.; February 2017. Available at: https://www.rexulti.com/. Accessed November 3, 2017.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: http://www.clinicalpharmacology-ip.com/.
3. American Psychiatric Association: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition, 2010. http://psychiatryonline.org/guidelines. Accessed November 2017.
4. American Psychiatric Association: Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition, 2004. http://psychiatryonline.org/guidelines. Accessed November 3, 2017.
5. American Psychiatric Association: Guideline Watch (September 2009): Practice Guideline for the Treatment of Patients with Schizophrenia, 2009. http://psychiatryonline.org/guidelines. Accessed November 3, 2017.
6. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull 2010 Jan; 36(1):71-93.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
New guideline created	09.15	11.15
Converted to new integrated template. Removed age requirement since not referenced in FDA indications section per PI; MDD: modified requirement for antidepressant trials to include duration of trial (≥ 4 weeks); Schizophrenia: modified requirement related to failure of 3 of the following atypical antipsychotic trials (risperidone, quetiapine, olanzapine, or ziprasidone) by increasing duration of trial from ≥ 2 weeks to ≥ 4 weeks and adding criteria regarding patients with diabetes or BMI > 30; also increased the duration of trial of aripiprazole to ≥ 4 weeks;	08.16	11.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Modified specific max quantity limit to FDA max recommended dose and health plan approved QL statement. Removed "New patients stable on Rexulti" under initial approval and incorporated continuity of care in continuation criteria; Updated references to reflect current literature search		
Converted to new template. Added age restriction per PI/safety approach. Updated max dose requirement to include specific QL. Schizophrenia: Modified requirement related to trial and failure of 3 atypical antipsychotics to 2 atypical antipsychotics since aripiprazole is available on the PDL as a generic and criteria require an additional trial of aripiprazole prior to approval of Rexulti. Removed requirement that trialed antipsychotics must be generic to give credit to members who have tried branded products. Re-auth: Removed MDD from COC criteria since the diagnosis is not eligible for COC.	08.08.17	11.17
1Q18 annual review: - Policy combined for Medicaid, marketplace and commercial lines of business - No significant change from previous corporate approved policy - HIM: added trial of aripiprazole - Commercial: added trial of aripiprazole as requirement for schizophrenia and increased overall drug trials from 2 drugs to 3. For depression changed from 2 trials of atypical antipsychotics to 3 trials of antidepressants and a trial of aripiprazole - References reviewed and updated.	11.13.17	02.18

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.