Clinical Policy: Brexpiprazole (Rexulti)

Reference Number: CP.PMN.68
Effective Date: 12.01.15
Last Review Date: 08.24
Line of Business: Commercial, HIM, 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) in adults
- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older
- Treatment of agitation associated with dementia due to Alzheimer's disease (AD)

Limitation of use: Rexulti is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to AD.

Policy/Criteria

Provider must submit documentation (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. Member meets one of the following (a or b):
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);
   b. Failure of THREE antidepressants from at least TWO different classes (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) at up to maximally indicated doses, each used for ≥ 4 weeks, unless member is unable to satisfy this requirement due to clinically significant adverse effects experienced, member's age ≥ 65 years, or contraindication(s) to multiple antidepressants;
4. Member meets one of the following (a or b):
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);

b. Failure of a ≥ 4-week trial of aripiprazole at up to maximally indicated doses, used concurrently with an antidepressant, unless contraindicated or clinically significant adverse effects are experienced;

5. Rexulti is prescribed concurrently with an antidepressant;
6. Dose does not exceed both of the following (a and b):
   a. 3 mg per day;
   b. 1 tablet per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Schizophrenia (must meet all)**:**

1. Diagnosis of schizophrenia;
2. Age ≥ 13 years;
3. Member meets one of the following (a, b, or c):
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);
   b. Failure of one of the following generic atypical antipsychotics at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: risperidone, quetiapine, olanzapine, ziprasidone;
   c. Member has diabetes mellitus or body mass index (BMI) > 30 kg/m^2;
4. Member meets one of the following (a or b):
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);
   b. Failure of a ≥ 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 both of the following (a and b):
   a. 4 mg per day;
   b. 1 tablet per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

C. Alzheimer's Disease Related Agitation

1. Diagnosis of agitation associated with dementia due to AD;
2. Age ≥ 18 years;
3. Rexulti is not prescribed as an as needed ("prn") treatment;
4. Dose does not exceed both of the following (a and b):
   a. 3 mg per day;
   b. 1 tablet per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

D. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 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, b, or c):
   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 or major depressive disorder and has received this medication for at least 30 days;
   c. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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 or AD related agitation (i and ii):
      i. 3 mg per day;
      ii. 1 tablet per day;
   b. Schizophrenia (i and ii):
      i. 4 mg per day;
      ii. 1 tablet per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 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.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents;

B. Dementia-related psychosis.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AD: Alzheimer's disease
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
Antipsychotics		
aripiprazole (Abilify®)	**Schizophrenia** Adults: 10 to 15 mg PO QD **Major Depressive Disorder** 5 to 10 mg PO QD	Schizophrenia: 30 mg/day Major Depressive Disorder: 15 mg/day
olanzapine (Zyprexa®)	**Schizophrenia**	20 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Initial: 5 to 10 mg PO QD; target: 10 mg PO QD	
quetiapine immediate-release (Seroquel®)	**Schizophrenia** Initial: 25 mg PO BID; target: 400 to 800 mg/day	800 mg/day
risperidone (Risperdal®)	**Schizophrenia** Initial: 1 mg PO BID or 2 mg PO QD; target: 4 to 8 mg PO QD	Schizophrenia Adolescents: 6 mg/day Adults: 16 mg/day
ziprasidone (Geodon®)	**Schizophrenia** 20 mg PO BID	160 mg/day
Selective Serotonin Reuptake Inhibitors (SSRIs)		
citalopram (Celexa®)	**Major Depressive Disorder** Refer to prescribing information	40 mg/day
escitalopram (Lexapro®)		20 mg/day
fluoxetine (Prozac®)		Immediate-release: 80 mg/day (20 mg/day if pediatric) Delayed-release: 90 mg/week
fluvoxamine* (immediate-release) (Luvox®)		150 mg/day
paroxetine (Paxil®, Paxil CR®, Pexeva®)		Immediate-release: 50 mg/day (40 mg/day if geriatric) Extended-release: 62.5 mg/day (50 mg/day if geriatric)
sertraline (Zoloft®)		200 mg/day (20 mg/day if age 6-11 years*)
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)		
desvenlafaxine (Pristiq®)	**Major Depressive Disorder** Refer to prescribing information	400 mg/day
duloxetine (Cymbalta®)		120 mg/day
Fetzima® (levomilnacipran)		120 mg/day
venlafaxine (Effexor®, Effexor XR®)		Extended-release: 225 mg/day
Tricyclic Antidepressant (TCAs)		
amitriptyline (Elavil®)	**Major Depressive Disorder** Refer to prescribing information	150 mg/day
amoxapine		400 mg/day (300 mg/day if geriatric)
clomipramine* (Anafranil®)		250 mg/day (200 mg/day if pediatric)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
desipramine (Norpramin®)		300 mg/day (100 mg/day if pediatric)
doxepin (Sinequan®)		300 mg/day
imipramine HCl (Tofranil®)		200 mg/day (150 mg/day if geriatric or pediatric)
imipramine pamoate (Tofranil PM®)		200 mg/day (100 mg/day if geriatric or pediatric)
nortriptyline (Pamelor®)		150 mg/day
protriptyline (Vivactil®)		60 mg/day (30 mg/day if geriatric or pediatric)
trimipramine (Surmontil®)		200 mg/day (100 mg/day if geriatric or pediatric)
Monoamine Oxidase Inhibitors		
isocarboxazid (Marplan®)	**Major Depressive Disorder** Refer to prescribing information	60 mg/day
phenelzine (Nardil®)		90 mg/day
selegiline (EMSAM® transdermal; Eldepryl®, Zelapar®, Carbex®)		Transdermal: 12 mg/24 hr Oral*: 30 mg/day
tranylcypromine (Parnate®)		60 mg/day
Other Antidepressants		
bupropion (Aplenzin®, Budeprion SR®, Budeprion XL®, Forfivo XL®, Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	**Major Depressive Disorder** Refer to prescribing information	Immediate-release: 450 mg/day (300 mg/day if pediatric) Sustained-release: 400 mg/day Extended-release (HCl): 450 mg/day Extended-release (HBr): 522 mg/day
mirtazapine (Remeron®)		45 mg/day
perphenazine/ amitriptyline (Triavil®)		16 mg/day perphenazine and 200 mg/day amitriptyline
maprotiline (Ludiomil®)		150 mg/day
nefazodone (Serzone®)		600 mg/day
trazodone (Desyrel®, Oleptro®)		Immediate-release: 400 mg/day Extended-release: 375 mg/day
vortioxetine (Trintellix®)		20 mg/day
vilazodone (Viibryd®)		40 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: Contraindications/Boxed Warnings

- Contraindication(s): known hypersensitivity to Rexulti or any of its components
- Boxed warning(s):
  - 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 without agitation associated with dementia due to Alzheimer's disease.
  - Antidepressants increase the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor all antidepressant-treated patients for clinical worsening and emergences of suicidal thoughts and behaviors. Safety and effectiveness of Rexulti have not been established in pediatric patients with MDD.

Appendix D: States with Limitations against Redirections in Certain Mental Health Settings

State	Step Therapy Prohibited?	Notes
AR	Yes	**Applies to HIM requests only** For the treatment of psychosis and serious mental illness through antipsychotic prescription drugs, no step therapies allowed.
NV	No	**Applies to Medicaid requests only** • **MDD**: Failure of aripiprazole or an antidepressant (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) at up to maximally indicated doses, used for ≥ 4 weeks, unless member is unable to satisfy this requirement due to clinically significant adverse effects experienced, member's age ≥ 65 years, or contraindication(s) to multiple antidepressants. • **Schizophrenia**: Failure of ONE of the following at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: aripiprazole, risperidone, quetiapine, olanzapine, ziprasidone
TX	No	**Applies to HIM requests only** • **MDD**: Failure of aripiprazole or an antidepressant (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) at up to maximally indicated doses, used for ≥ 4 weeks, unless member is unable to satisfy this requirement due to clinically significant adverse effects experienced, member's age ≥ 65 years, or contraindication(s) to multiple antidepressants. • **Schizophrenia**: Failure of ONE of the following at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: aripiprazole, risperidone, quetiapine, olanzapine, ziprasidone

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Adjunctive treatment of MDD	0.5 mg or 1 mg PO QD, up to target dosage of 2 mg once daily	3 mg/day
Schizophrenia	Adults: 1 mg PO QD, up to target dosage of 2 mg to 4 mg once daily Pediatric (13-17 years): 0.5 mg PO QD, up to target dosage of 2 mg to 4 mg once daily	4 mg/day
Agitation associated with dementia due to AD	0.5 mg PO QD, up to target dosage of 2 mg once daily	3 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, 4 mg

VII. References

1. Rexulti Prescribing Information. Rockville, MD: Otsuka America Pharmaceutical, Inc.; May 2024. Available at: https://www.rexulti.com/. Accessed May 9, 2024.
2. Clinical Pharmacology [database online]. Tampa FL: Gold Standard.; 2023. Available at: http://www.clinicalpharmacology-ip.com/. Accessed June 7, 2024.
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4. Qaseeem A, Owens DK, Etxeandia-Ikobaltzeta I, et al. Nonpharmacological and pharmacologic treatments of adults in the acute phase of major depressive disorder: A living clinical guideline from the American College of Physicians. Annals of Internal Medicine. February 2023; 172(2):239-253.
5. American Psychiatric Association: Guideline watch (September 2009): Practice guideline for the treatment of patients with schizophrenia, 2009. http://psychiatryonline.org/guidelines. Accessed May 8, 2023.
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.
7. Keepers G, Fochtmann L, Anzia J, et al. APA Practice guideline for the treatment of patients with schizophrenia, third edition. Am J Psychiatry. 2020 Sept;177(9):868-872.
8. Reus VJ, Fochtmann LJ, Eyler AE, et al. APA Practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. Am J Psychiatry. 2016 May;173(3):543-6. Available online at: https://psychiatryonline.org/doi/epdf/10.1176/appi.books.9780890426807. Accessed May 17, 2023.

9. Maglione M, Maher AR, Hu J, et al. Off-label use of atypical antipsychotics: An update. Rochkville (MD): Agency for Healthcare Research and Quality; 2011 Sept. (Comparative Effectiveness Reviews, No. 43). Available online at: https://www.ncbi.nlm.nih.gov/books/NBK66081/ Accessed May 17, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2020 annual review: no significant changes; references reviewed and updated.	11.30.19	02.20
Allowed members 65 years old or older to bypass redirections to TCA for major depressive disorder.	03.27.20	08.20
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	11.29.20	02.21
1Q 2022 annual review: no significant changes; revised Commercial approval duration from Length of Benefit to 12 months or duration of request, whichever is less; references reviewed and updated. RT4: updated age limit for schizophrenia per newly FDA-approved pediatric indication extension to patients 13-17 years of age.	11.13.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.10.22	
1Q 2023 annual review: no significant changes; added dementia related psychosis to Section III; updated boxed warnings per PI; references reviewed and updated.	11.03.22	02.23
Added redirection bypass for members in a State with limitations on step therapy in certain mental health settings along with Appendix D, which includes Arkansas.	07.05.23	
3Q 2023 annual review: no significant changes; references reviewed and updated. RT4: new indication added for treatment of agitation associated with dementia due to AD. Added Texas to Appendix D with requirements for single drug redirection for HIM requests.	07.13.23	08.23
Added Nevada to Appendix D with requirements for single drug redirection for Medicaid requests.	08.31.23	
3Q 2024 annual review: for Schizophrenia, changed to "failure of one of the following generic atypical antipsychotics…" (previously was failure of two) to align with other atypical antipsychotics; revised continued therapy criteria to allow continuity of care for MDD; for Appendix C, updated boxed warnings language to align with prescriber information; references reviewed and updated.	05.09.24	08.24

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.

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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.

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