Clinical Policy Title:	brexpiprazole
Policy Number:	RxA.468
Drug(s) Applied:	Rexulti®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Brexpiprazole (Rexulti®) is an atypical antipsychotic. Brexpiprazole is indicated for the:

- Adjunctive treatment of major depressive disorder (MDD)
- Treatment of schizophrenia.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
brexpiprazole (Rexulti®)	Adjunctive treatment of MDD	0.5 mg or 1 mg PO once daily, up to the target dosage of 2 mg once daily	3 mg/day
	Schizophrenia	1 mg PO once daily, up to the 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.

Dosage Forms

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

Clinical Policy

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

I. Initial Approval Criteria

A. Major Depressive Disorder (must meet all):

1. Diagnosis of MDD;
2. Age 18 years of age or older;
3. Failure of three antidepressants (e.g., selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], tricyclic antidepressant [TCA], bupropion, mirtazapine) from

at least two different classes at up to maximally indicated doses, each used for 4 weeks or longer, unless member is unable to satisfy this requirement due to clinically significant adverse effects or contraindications to antidepressants;
4. Failure of a 4-week trial or greater of a generic atypical antipsychotic (e.g., aripiprazole) at up to maximally indicated doses, used concurrently with an antidepressant, unless contraindicated or clinically significant adverse effects are experienced;
5. Brexpiprazole is prescribed concurrently with an antidepressant;
6. Dose does not exceed 3 mg (1 tablet) per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

B. Schizophrenia (must meet all):
1. Diagnosis of schizophrenia;
2. Age 18 years of age or older;
3. Failure of two of the following generic atypical antipsychotics: risperidone, quetiapine, olanzapine, or ziprasidone at up to maximally indicated doses, each used for 4 weeks or longer, unless all are contraindicated or clinically significant adverse effects are experienced;
4. Failure of a 4-week trial or greater of a generic atypical antipsychotic (e.g., aripiprazole) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 4 mg (1 tablet) per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):
1. Member meets one of the following (a or b):
   a. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy.
   b. Documentation supports that the member is currently receiving Rexulti® for adjunctive treatment of MDD and has received this medication for at least 30 days;
   c. 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 (1 tablet) per day;
   b. Schizophrenia: 4 mg (1 tablet) per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
BMI: body mass index
CrCl: creatinine clearance
CYP: cytochrome P450

FDA: Food and Drug Administration
MDD: major depressive disorder
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressants
SNRI: serotonin-norepinephrine reuptake inhibitors

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
Antipsychotics		
aripiprazole (Abilify®)	**Schizophrenia** Adults: 10 to 15 mg PO once daily **Major Depressive Disorder** 5 to 10 mg PO once daily	Schizophrenia: 30 mg/day Major Depressive Disorder: 15 mg/day
olanzapine (Zyprexa®)	**Schizophrenia** Initial: 5 to 10 mg PO once daily; target: 10 mg PO once daily	20 mg/day
quetiapine immediate-release (Seroquel®)	**Schizophrenia** Initial: 25 mg PO twice daily; target: 400 to 800 mg/day	800 mg/day
risperidone (Risperdal®)	**Schizophrenia** Initial: 1 mg PO twice daily or 2 mg PO once daily; target: 4 to 8 mg PO once daily	Adolescents: 6 mg/day Adults: 16 mg/day
ziprasidone (Geodon®)	**Schizophrenia** 20 mg PO twice daily	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

Drug Name	Dosing Regimen	Maximum Dose
fluoxetine (Prozac®)	**Major Depressive Disorder** Refer to prescribing information	Immediate-release: 80 mg/day (20 mg/day if pediatric) Delayed-release: 90 mg/week
fluvoxamine* (immediate-release)	**Major Depressive Disorder** Refer to prescribing information	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 XR®)		Extended-release: 225 mg/day
Tricyclic Antidepressant (TCAs)		
amitriptyline	**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)
desipramine (Norpramin®)		300 mg/day (100 mg/day if pediatric)
doxepin (Sinequan®)		300 mg/day

Drug Name	Dosing Regimen	Maximum Dose
imipramine HCl	**Major Depressive Disorder** Refer to prescribing information	200 mg/day (150 mg/day if geriatric or pediatric)
imipramine pamoate		200 mg/day (100 mg/day if geriatric or pediatric)
nortriptyline (Pamelor®)		150 mg/day
protriptyline		60 mg/day (30 mg/day if geriatric or pediatric)
trimipramine		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; Zelapar®)		Transdermal: 12 mg/24 hr Oral*: 30 mg/day
tranylcypromine (Parnate®)		60 mg/day
Other Antidepressants		
bupropion (Aplenzin®), Forfivo XL®, 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
Drug Name	**Dosing Regimen**	**Maximum Dose**
perphenazine/ amitriptyline	**Major Depressive Disorder** Refer to prescribing information	16 mg/day perphenazine and 200 mg/day amitriptyline
maprotiline		150 mg/day
nefazodone		600 mg/day
trazodone		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.
  - 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.

APPENDIX D: General Information

None.

References

1. Rexulti® Prescribing Information. Rockville, MD: Otsuka America Pharmaceutical, Inc.; March 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205422s005lbl.pdf. Accessed October 12, 2020.
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4. American Psychiatric Association: Practice Guideline for the Treatment of Patients with Schizophrenia, Second Edition, 2004. http://psychiatryonline.org/guidelines.
5. American Psychiatric Association: Guideline Watch (September 2009): Practice Guideline for the Treatment of Patients with Schizophrenia, 2009. http://psychiatryonline.org/guidelines.
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. Accessed October 12, 2020.
7. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Schizophrenia, Third Edition, 2020. Doi: 10.1176/appi.books.9780890424841. Accessed November 1, 2020.
8. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. The Lancet. 2019 Dec; 7(1):64-77. Accessed November 2, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Line of business policy applies was updated to “all lines of business”. 2. Initial approval criteria I.B.3 updated to remove requirement of patient having diabetes mellitus and BMI > 30. 3. Approval duration for commercial was updated from “length of benefit” to “12 months” for initial and continued therapy criteria. 4. HIM was removed from initial and continued therapy approval. 5. Continued therapy criteria II.A.1 was rephrased to “Currently receiving medication that has been authorized by RxAdvance…”. 6. Appendix B standard verbiage has been changed and updated. Also updated to remove discontinued drugs. 7. References were updated.	11/02/2020	12/07/2020