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PHARMACY POLICY – 5.01.659

Antipsychotics

Effective Date:	Jun. 1, 2026	RELATED MEDICAL POLICIES:	
Last Revised:	May 12, 2026	5.01.520	Antidepressants: Pharmacy Medical Necessity Criteria for Brands
		5.01.605	Medical Necessity Criteria for Pharmacy Edits

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Introduction

Antipsychotic medications are a class of drugs primarily used to treat acute psychosis (regardless of cause) and chronic psychotic disorders such as schizophrenia. They are also effective for managing acute agitation, bipolar mania, and several other psychiatric conditions. First-generation antipsychotics (FGAs), sometimes called "typical" antipsychotics, were the original drugs developed for psychosis. They are effective but are associated with a higher risk of movement-related side effects, such as extrapyramidal symptoms (EPS) and tardive dyskinesia. Second-generation antipsychotics, also known as "atypical" antipsychotics, generally have a lower risk of EPS and tardive dyskinesia compared to FGAs. This policy describes when second-generation antipsychotics may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
• **Abilify (aripiprazole)** • **Brand quetiapine** • **Caplyta (lumateperone)** • **Clozaril (clozapine)** • **Fanapt (iloperidone)** • **Geodon (ziprasidone) oral** • **Invega (paliperidone)** • **Latuda (lurasidone)** • **Lybalvi (olanzapine and samidorphan)** • **Risperdal (risperidone)** • **Saphris (asenapine)** • **Secuado (asenapine transdermal)** • **Seroquel (quetiapine)** • **Seroquel XR (quetiapine extended release)** • **Versacloz (clozapine)** • **Vraylar (cariprazine)** • **Zyprexa (olanzapine)** • **Zyprexa Zydis (olanzapine)**	**Brand second-generation antipsychotics may be considered medically necessary when:** • The individual has tried 1 generic second-generation antipsychotic (e.g., aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) and had an inadequate response or intolerance **Note:** Only applies to individuals not previously treated with requested therapy.
Cobenfy (xanomeline and trospium chloride)	**Cobenfy (xanomeline and trospium chloride) may be considered medically necessary for the treatment of schizophrenia when all the following are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with schizophrenia based on the most updated Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria **AND** • Has tried 3 generic second-generation antipsychotics (e.g., aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) and had an inadequate response or intolerance **AND** • Prescribed by or in consultation with a psychiatrist **AND** • The dose is limited to 125 mg/30 mg capsule twice daily

Drug	Medical Necessity
Latuda (lurasidone HCL)	**Latuda (lurasidone HCL) may be considered medically necessary for the treatment of bipolar depression when:** • The individual has tried generic lurasidone and had an inadequate response or intolerance
Nuplazid (pimavanserin)	**Nuplazid (pimavanserin) may be considered medically necessary for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.** **Note:** Nuplazid is not subject to the criteria of other brand name second generation antipsychotics outlined above, and its use is restricted to individuals with Parkinson's disease psychosis only.
Opipza (aripiprazole oral film)	**Opipza (aripiprazole oral film) may be considered medically necessary when all the following are met:** • The individual has tried 1 generic second-generation antipsychotics (e.g., aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) and had an inadequate response or intolerance **OR** • Documentation is provided that the oral film is clinically necessary (e.g., trouble swallowing, etc.) **AND** • The dose is limited to 30 mg per day
Rexulti (brexpiprazole)	**Rexulti (brexpiprazole) may be considered medically necessary when:** • The individual has tried aripiprazole and had an inadequate response or intolerance **Rexulti (brexpiprazole) may be considered medically necessary for the treatment of agitation associated with dementia due to Alzheimer's disease when the following criteria are met:** • The individual has agitation (e.g., pacing, gesturing, profanity, shouting, shoving, hitting) associated with dementia due to Alzheimer's disease (documentation required) **AND** • The dose is limited to 3 mg once daily

Drug	Medical Necessity
	Note: Rexulti is not approved for the treatment of individuals with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease (boxed warning).
Symbyax (fluoxetine-olanzapine)	**Symbyax (fluoxetine-olanzapine) may be considered medically necessary when:** • The individual has tried generic fluoxetine-olanzapine and had an inadequate response or intolerance
Vraylar (cariprazine)	**Vraylar (cariprazine) may be considered medically necessary for the treatment of bipolar depression when all the following are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with bipolar depression **AND** • Has tried quetiapine, lurasidone, or olanzapine-fluoxetine combination and had an inadequate response or intolerance

Drug	Investigational
As listed	**Use of the drugs for conditions not listed in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information unless noted otherwise for the medication under the medical necessity criteria.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All reviews for all drugs listed in this policy may be approved up to 12 months.**
Re-authorization criteria	**All reviews for all drugs listed in this policy may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

N/A

Related Information

Consideration of Age

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

Benefit Application

The drugs in this policy are oral medications and managed through the pharmacy benefit.

Evidence Review

Summary of Evidence

Cobenfy (xanomeline and trospium chloride)

Cobenfy (xanomeline and trospium chloride) is an oral first-in-class muscarinic agonist for the treatment of schizophrenia in adults. It combines xanomeline, an M1/M4 muscarinic receptor agonist, with trospium chloride, a muscarinic receptor antagonist that offsets the peripheral

effects of xanomeline and does not appreciably cross the blood-brain barrier. Approval was based on data from the EMERGENT clinical program, which includes three placebo-controlled studies and two open-label trials assessing long-term safety and tolerability of Cobenfy for up to 1 year. The Phase 3 EMERGENT-2 and EMERGENT-3 trials demonstrated that Cobenfy significantly reduced schizophrenia symptoms compared to the placebo. Unlike first- and second-generation antipsychotics (SGAs), which are associated with adverse events including extrapyramidal symptoms, weight gain, QTc prolongation, and an increased risk for diabetes, the Cobenfy Phase 3 studies consistently found no significant changes in weight, lipid levels, glucose, insulin, or alertness. The most common adverse reactions with Cobenfy therapy (≥5% and at least twice the rate of placebo) were nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease. Cobenfy's label does not carry antipsychotic class warnings or precautions, and it does not include a Boxed Warning. However, it is contraindicated in individuals with urinary retention, moderate or severe kidney or liver disease, gastric retention, untreated narrow-angle glaucoma, or a history of hypersensitivity to Cobenfy or its components.

Bipolar Depression

The other established medications for the treatment of bipolar depression are more problematic for the following reasons:

- Symbyax: The fixed dose combination makes dose adjustments difficult, and olanzapine metabolic side-effects are considerably more problematic than Latuda or Seroquel XR.
- Lithium: Multiple daily dosing needed, plus small window between therapeutic and toxic serum levels, plus more problematic side-effects, plus augmentation with an SGA antipsychotic is not infrequently needed.
- Lamotrigine: Multiple daily dosing needed, plus risk of Stevens-Johnson (SJ) syndrome (and have to d/c with any rash, even if eventually not SJ syndrome), plus sub-optimal efficacy for acute depressive symptoms.
- Immediate-release quetiapine: Multiple daily dosing needed, plus more sedating than Latuda, plus XR formulation has a "smoother" clinical effect.

Parkinson’s Disease Psychosis

Psychotic symptoms in Parkinson's disease (PD) are relatively common and, in addition to creating a disturbance in individuals' daily lives, have consistently been shown to be associated with poor outcome. Our understanding of the pathophysiology of psychosis in PD has expanded dramatically over the past 15 years, from an initial interpretation of symptoms as dopaminergic drug adverse effects to the current view of a complex interplay of extrinsic and disease-related factors. PD psychosis has unique clinical features, namely that it arises within a context of a clear sensorium and retained insight, there is relative prominence of visual hallucinations and progression occurs over time. PD psychosis tends to emerge later in the disease course, and disease duration represents one risk factor for its development. The use of anti-PD medications (particularly dopamine receptor agonists) has been the most widely identified risk factor for PD psychosis. Other risk factors discussed in the literature include older age, disease severity, sleep disturbance, cognitive impairment, dementia and/or depression.

Traditionally, treatment begins with a search for correctable infectious, toxic, and metabolic etiologies. If symptoms persist, anti-Parkinson's disease medications are slowly reduced. However, withdrawal of these drugs usually worsens parkinsonism and is often not tolerated. Certain atypical antipsychotics can be used to treat psychosis without compromising motor function. The choice of atypical antipsychotics is largely based on ease of use and adverse effect profile as most have comparable efficacy in improving psychosis.

At the time of this update, Nuplazid is the first FDA-approved treatment for hallucinations and delusions associated with Parkinson’s disease psychosis.

References

1. Nussbaum A, Stroup TS. Paliperidone for Schizophrenia. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006369.
2. Komossa K, Rummel-Kluge C, Schwarz S, et.al. Risperidone versus Other Atypical Antipsychotics for Schizophrenia. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD006626.
3. Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine versus Other Atypical Antipsychotics for Schizophrenia. Cochrane Database Syst Rev. 2010 Mar 17;(3):CD006654.
4. Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone versus Other Atypical Antipsychotics for Schizophrenia. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006627.
5. Komossa K, Rummel-Kluge C, Schmid F, et al. Aripiprazole versus Other Atypical Antipsychotics for Schizophrenia. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006627.

6. Manual of Clinical Psychopharmacology, 6th edition; Schatzberg, Cole, and DeBattista; American Psychiatric Publishing, 2007 (7th edition due out in 2010).
7. Evidence-Based Psychopharmacology; Stein, Lerer, and Stahl (editors); Cambridge University Press, 2005.
8. Product information for Nuplazid (pimavanserin). Revised January 2025, Acadia Pharmaceuticals, San Diego, CA. Available at: **https://www.nuplazid.com/pdf/nuplazid-prescribing-information.pdf**. Accessed January 6, 2026.

History

Date	Comments
01/01/26	New policy, approved December 9, 2025. Add to Prescription Drug section. Moved coverage criteria for all Antipsychotics (Second Generation, "Atypicals"), Brands from policy 5.01.605 to policy 5.01.659 Antipsychotics. New policy sections for Metallic (individual/small group/student ISHIP) formulary plans, Essentials formulary plans, and Open/Preferred/Select formulary plans and plans with no pharmacy benefit coverage. Added different coverage criteria for Metallic (individual/small group/student ISHIP) formulary and Essentials formulary plans for Second Generation Antipsychotics. Removed brand clozapine and brand clozapine ODT as drugs are no longer on the market. Removed Mezofy (aripiprazole) as drug has been discontinued.
02/01/26	Annual Review, approved January 13, 2026. Updated for all sections the Symbyax (fluoxetine-olanzapine) criteria to require the individual tried fluoxetine-olanzapine and had an inadequate response or intolerance. Updated for all sections the Vraylar (cariprazine) criteria for the treatment of bipolar depression to require the individual tried quetiapine, lurasidone, or olanzapine-fluoxetine combination and had an inadequate response or intolerance.
06/01/26	Interim Review, approved May 12, 2026. Updated formatting removing the reference to Section 1: Open, Preferred, and Select Formulary Plans (Rx Plan A1, A2, B3, B4, C4, and F1) and Plans with No Pharmacy Benefit Coverage ONLY. Removed the following: Section 2: Essentials Formulary Plans (Rx Plan E1, E3, E4) and Plans with the High Cost Low Value Drug List and Section 3 Individual/Small Group/Student ISHIP Metallic Formulary Plans (Rx Plan M1, M2, and M4). Removed reference to non-formulary exception reviews.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.