BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

COBENFY™ (xanomeline and trospium chloride) oral capsule Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for COBENFY (xanomeline and trospium chloride) oral capsule

Criteria for Initial Therapy:

Prescriber Qualifications
- A physician specializing in schizophrenia or in consultation with a Psychiatrist

Indication
- Schizophrenia

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Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Diagnosis established by psychiatric examination based on DSM 5 criteria
- Experiencing acute exacerbation or relapse of psychotic symptoms with onset less than two months
- Requires hospitalization for acute exacerbation or relapse or is inpatient transitioning to discharge
- Not newly diagnosed with schizophrenia or experiencing a first treated episode of schizophrenia
- Does not have treatment resistant schizophrenia
- Positive and Negative Syndrome Scale (PANSS) total score between 80 and 120
- PANSS score of 4 or greater(moderate or greater) for at least **TWO** of the following Positive Scale (P) items:
  - Item 1 (P1: Delusions)
  - Item 2 (P2: Conceptual disorganization)
  - Item 3 (P3: Hallucinatory behavior)
  - Item 6 (P6: Suspiciousness/persecution)
- Clinical Global Impression–Severity (CGI S) score of 4 or higher
- Liver enzymes and bilirubin
- Heart rate

Alternative Therapies

- Failure, contraindication per FDA label, intolerance, or not a candidate for **ONE** of the following:
  - Aripiprazole
  - Risperidone
  - Olanzapine
  - Clozapine
  - Quetiapine

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with another anticholinergic medication
- No FDA label contraindications:
  - Urinary retention
  - Moderate or severe hepatic impairment (Child Pugh Class B or C)
  - Gastric retention
  - Untreated narrow angle glaucoma
  - History of hypersensitivity to Cobenfy or trospium chloride

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- Does not have any degree of hepatic impairment
- Does not have active biliary disease
- Does not have moderate or severe renal impairment (estimated glomerular filtration rate less than 60 mL/min)

Documentation Requirements

- Completed request form including:
  - Chart notes
  - Lab results
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications

- Continues to be seen by a physician specializing in schizophrenia or in consultation with a Psychiatrist

Clinical Response

- Positive clinical response defined as **BOTH:**
  - Improved PANSS over baseline
  - Improved CGI S score over baseline

Adherence

- Adherence to prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No new contraindications or significant adverse drug effects such as:
  - Urinary retention
  - Moderate or severe hepatic impairment (Child Pugh Class B or C)
  - Gastric retention
  - Untreated narrow angle glaucoma
  - History of hypersensitivity to Cobenfy or trospium chloride
  - Liver injury (e.g., jaundice, pruritus, ALT greater than five times upper limit of normal or baseline)

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  - Angioedema
  - Dizziness, confusion, hallucinations, somnolence
- No concomitant use with another anticholinergic medication
- Does not have any degree of hepatic impairment
- Does not have active biliary disease
- Does not have moderate or severe renal impairment (estimated glomerular filtration rate less than 60 mL/min)

Documentation Requirements

- Chart notes
- Lab values confirming safe use
- Supporting clinical documentation with evidence of improvement

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Cobenfy (xanomeline and trospium chloride) is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist, indicated for the treatment of schizophrenia in adults. The mechanism of action of xanomeline in the treatment of schizophrenia is unclear; however, its efficacy is thought to be due to its agonist activity at M1 and M4 muscarinic acetylcholine receptors in the central nervous system. Trospium chloride is a muscarinic antagonist. Trospium chloride antagonizes the muscarinic receptors primarily in the peripheral tissues. Trospium chloride is a quaternary ammonium compound.

The efficacy of Cobenfy for the treatment of schizophrenia in adults was evaluated in two placebo-controlled studies with identical designs (N = 470). Study 1 (NCT04659161) and Study 2 (NCT04738123) were five-week, randomized, double-blind, placebo controlled, multi-center studies in adult individuals with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual – Fifth edition (DSM-5) criteria. Individuals were randomized to Cobenfy or placebo.

The primary efficacy measure was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 5. The PANSS is a 30-item scale that measures symptoms of schizophrenia. Each item is rated by a clinician on a seven-point scale. A score of 1 indicates the absence of symptoms, and a score

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of 7 indicates extremely severe symptoms. The PANSS total score may range from 30 to 210 with higher scores reflecting greater overall symptom severity.

In Study 1 and Study 2, individuals randomized to Cobenfy showed a statistically significant reduction from baseline to Week 5 in the PANSS Total Score compared to the placebo group. A secondary endpoint, the change from baseline to Week 5 on the Clinical Global Impression–Severity (CGI-S) score, was statistically significant for Cobenfy compared to placebo in Study 1. The CGI-S is a validated clinician-rated scale that measures the individual's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale. Examination of subgroups by age, sex, and race did not suggest differences in response in the study, there were no Individuals over 65 years of age.

The primary efficacy endpoint placebo-subtracted difference for Cobenfy in PANSS for individuals at week 5 in Study 1 was -9.6 and for Study 2 was -8.4, both were statistically significantly superior to placebo.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Acute phase:

- The phase of schizophrenia when a person experiences an increase in distressing symptoms

Maintenance phase:

- The phase of treatment when antipsychotic drug regimens are administered to limit the frequency and severity of relapses and maximize the effects of treatment on symptoms

Treatment resistant schizophrenia:

- Nonresponse to at least two sequential antipsychotic trials of sufficient dose, duration, and adherence

Positive and Negative Syndrome Scale (PANSS)

Please rate each item on the PANSS using the following scale		
1 - absent, **2** - minimal, **3** - mild, **4** - moderate, **5** - moderate severe, **6** - severe, **7** - extreme		
		Indicate score: 1, 2, 3, 4, 5, 6, or 7
P1	Delusions	
P2	Conceptual disorganization	
P3	Hallucinatory behavior	
P4	Excitement	
P5	Grandiosity	
P6	Suspiciousness/persecution	
P7	Hostility	
N1	Blunted affect	
N2	Emotional withdrawal	
N3	Poor rapport	
N4	Passive/apathetic social withdrawal	

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N5	Difficulty in abstract thinking	
N6	Lack of spontaneity and flow of conversation	
N7	Stereotyped thinking	
G1	Somatic concern	
G2	Anxiety	
G3	Guilt feelings	
G4	Tension	
G5	Mannerisms and posturing	
G6	Depression	
G7	Motor retardation	
G8	Uncooperativeness	
G9	Unusual thought content	
G10	Disorientation	
G11	Poor attention	
G12	Lack of judgment and insight	
G13	Disturbance of volition	
G14	Poor impulse control	
G15	Preoccupation	
G16	Active social avoidance	

Scoring: ranges 30 to 210 with higher scores reflecting greater overall symptom severity	
Total score:	
Positive (P) scale score:	
Negative (N) scale score:	
General (G) psychopathology scale score:	

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261–276. https://doi.org/10.1093/schbul/13.2.261

Clinical global impression – severity (CGI-S) score

	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients

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Clinical global impression – improvement (CGI-I) score

1	Very much improved
2	Much improved
3	Minimally improved
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

Resources:

Cobenfy (xanomeline and trospium chloride) product information, revised by E. R. Squibb & Sons, LLC. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 26, 2025.

Fischer BA, Buchanan RW. Schizophrenia in adults: Clinical features, assessment, and diagnosis. In: UpToDate, Marder S, Friedman M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic last updated March 14, 2025. Accessed September 19, 2025.

Marder S. Psychosis in adults: Initial management. In: UpToDate, Stein MB, Friedman M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic last updated November 13, 2024. Accessed September 19, 2025.

Stroup TS, Marder S. Schizophrenia in adults: Maintenance therapy and side effect management. In: UpToDate, Stein MB, Friedman M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic last updated August 05, 2024. Accessed September 19, 2025.

Kane J, Rubio JM, Kishimoto T, Correll CU. Treatment-resistant schizophrenia. In: UpToDate, Marder S, Friedman M (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic last updated August 15, 2024. Accessed September 19, 2025.

Tice JA, Whittington MD, McKenna A, et al.: KarXT for Schizophrenia: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, January 25, 2024. https://icer.org/assessment/schizophrenia-2024/#overview. Accessed October 29, 2024. Re-evaluated September 19, 2025.

Kaul I, Sawchak S, Correll CU, et al.: Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline–trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomized, double-blind, placebo-controlled, flexible-dose phase 3 trial. Lancet 2024; 403: 160–70. Accessed October 28, 2024. Re-evaluated September 19, 2025.

Kaul I, Sawchak S, Walling DP, et al.: Efficacy and Safety of Xanomeline-Trospium Chloride in Schizophrenia: A Randomized Clinical Trial. JAMA Psychiatry 2024 August; 81(8):749-756. Accessed October 28, 2024. Re-evaluated September 19, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04659161: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults With DSM-5 Schizophrenia. Available from: http://clinicaltrials.gov. Last update posted December 12, 2023. Last verified November 2023. Accessed October 28, 2024. Re-evaluated September 19, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04738123: A Phase 3, Randomized, Double-blind, Parallel-group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of KarXT in Acutely Psychotic Hospitalized Adults With DSM-5 Schizophrenia. Available from: http://clinicaltrials.gov. Last update posted October 31, 2023. Last verified October 2023. Accessed October 28, 2024. Re-evaluated September 19, 2025.

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