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 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.

Criteria:

➢ **Criteria for initial therapy:** Cobenfy (xanomeline and trospium chloride) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist

2. Individual is 18 years of age or older

3. Individual has a confirmed primary diagnosis of schizophrenia and is experiencing an acute exacerbation or relapse of psychotic symptoms with an onset of less than 2-months prior

4. Individual requires hospitalization for this acute exacerbation or relapse of psychotic symptoms or is already an inpatient where the requested agent was started and now is transitioning to discharge

5. Individual has Positive and Negative Syndrome Scale total score between 80 and 120, inclusive, with score of ≥ 4 (moderate or greater) for ≥ 2 of the following Positive Scale (P) items:
    a. Item 1 (P1; delusions)
    b. Item 2 (P2; conceptual disorganization)
    c. Item 3 (P3; hallucinatory behavior)
    d. Item 6 (P6; suspiciousness/persecution)

6. Individual has a Clinical Global Impression–Severity (CGI-S) score of 4 or higher

7. Individual is **not** newly diagnosed with schizophrenia or experiencing a first treated episode of schizophrenia

8. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Diagnosis established by psychiatric examination based on DSM-5 criteria
    b. Liver enzymes and bilirubin
    c. Heart rate

9. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

10. Individual does not have treatment-resistant schizophrenia

11. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** the following:
    a. Aripiprazole
    b. Risperidone
    c. Olanzapine
    d. Clozapine
    e. Quetiapine

12. Individual is not currently taking any other drug that may cause a severe adverse reaction or any significant drug interaction that may require discontinuation such as use with another anticholinergic medication

13. There are **NO** FDA-label contraindications such as:
    a. Urinary retention
    b. Moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment
    c. Gastric retention
    d. Untreated narrow-angle glaucoma
    e. History of hypersensitivity to Cobenfy or trospium chloride

14. Individual does not have any degree of hepatic impairment

15. Individual does not have active biliary disease

16. Individual does not have moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <60 mL/min)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cobenfy (xanomeline and trospium chloride) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist

2. Individual's condition has responded while on therapy with response defined as **BOTH** of the following:
    a. Improved PANSS over baseline
    b. Improved Clinical Global Impression–Severity (CGI-S) score over baseline

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindication or other significant adverse drug effect that may exclude continued use such as:
    a. Liver injury such as jaundice, pruritus, or alanine aminotransferase levels more than five times the upper limit of normal or five times baseline values
    b. Angioedema of the face, lips, tongue, and/or larynx
    c. Dizziness, confusion, hallucinations, and somnolence

6. Individual is not currently taking any other drug that may cause a severe adverse reaction or any significant drug interaction that may require discontinuation such as use with another anticholinergic medication

7. Individual does not have any degree of hepatic impairment

8. Individual does not have active biliary disease

9. Individual does not have moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <60 mL/min)

Renewal duration: 12 months

- 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 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	
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

1	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

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 October 28, 2024.

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 September 2024. Topic last updated July 05, 2023. Accessed October 29, 2024.

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 September 2024. Topic last updated August 06, 2024. Accessed October 29, 2024.

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 September 2024. Topic last updated June 27, 2024. Accessed October 29, 2024.

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 September 2024. Topic last updated August 15, 2024. Accessed October 29, 2024.

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.

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.

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.

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.

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.