Annual National Student Pharmacist P&T COMPETITION EST. 2000

AMCP Foundation

Drug Monograph

Team 27000

Patients First Health Plan
Formulary Drug Monograph
Individual Drug Review: Lynkuet® (elinzanetant)

Executive Summary

- Xanomeline/trospium chloride is a combination agent and the first selective muscarinic antipsychotic indicated for schizophrenia in adults.
- Two placebo-controlled studies showed statistically significant differences in symptom severity reductions measured via PANSS total score in Cobenfy (−20 to −21 points) vs placebo (−11 to −12).
- An ICER network meta-analysis showed no significant differences in efficacy compared to three commonly prescribed atypical antipsychotics (also known as second-generation antipsychotics).
- Indirect comparisons show no significant differences in efficacy, but less weight gain than olanzapine and risperidone.
- Advantages include lack of metabolic ADRs and movement side effects.
- Limitations include lack of long-term safety data, twice daily dosing, use in highly generic class, and lack of comparator studies.
- Place in therapy likely for patients with significant metabolic concerns or after failure of other atypical antipsychotics.

Recommendation
May include, Tier 3, ST, PA, QL

Rationale
Despite having a novel mechanism, there are numerous cost-effective, generically available therapeutic alternatives. Evidence consists of two placebo-controlled studies and no head-to-head studies. Using an indirect comparison, Cobenfy demonstrated a similar reduction in PANSS scores vs. alternatives. Limitations include twice daily dosing and significant discontinuation rate in studies due to ADRs.

Abbreviations used in this monograph			
ADR	adverse drug reaction	PANSS	Positive and Negative Syndrome Scale
CNS	central nervous system	PMPM	per member per month
EPS	extrapyramidal symptoms	QALYs	quality-adjusted life years
ICER	Institute for Clinical and Economic Review	WAC	wholesale acquisition cost
LFTs	liver function tests		

Product Information

All information is from the Cobenfy prescribing information[1] unless otherwise noted.

Brand (generic)	Cobenfy (xanomeline/trospium chloride)
Manufacturer	Bristol-Myers Squibb
Indication(s)	Treatment of schizophrenia in adults
Mechanism of action	• Combination of muscarinic agonist (xanomeline) and muscarinic antagonist (trospium chloride) • M1 and M4 agonism in the CNS modulating dopaminergic, glutamatergic, and GABAergic neurotransmission indirectly; this mechanism is independent of D2 receptor blockade
Dosage/ administration	• Recommended starting dose 50 mg/20 mg orally twice daily for at least two days, then increase to 100 mg/20 mg twice daily for at least five days • May be increased to 125 mg/30 mg orally twice daily based on patient tolerability and response • Assess LFTs, bilirubin, and heart rate prior to initiating therapy and when clinically indicated
Dosage forms/ strengths	Capsules: 50 mg/20 mg, 100 mg/20 mg, 125 mg/30 mg (xanomeline/trospium chloride content)
Contraindications	Urinary retention, moderate or severe hepatic impairment, gastric retention, history of hypersensitivity to xanomeline or trospium chloride, or untreated narrow-angle glaucoma
Warnings/ precautions	• Urinary retention • Use in patients with hepatic or renal impairment, biliary disease, or narrow-angle glaucoma • Decreased gastrointestinal motility • Angioedema • Increases in heart rate • CNS effects
Adverse reactions	Most common (≥ 5% and at least twice placebo): nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, gastrointestinal reflux disease
Drug interactions	• Drugs eliminated by active tubular secretion: Monitor for increased frequency and/or severity of ADRs • Strong CYP2D6 inhibitors: Monitor for increased frequency and/or severity of ADRs • Sensitive substrates of CYP3A4 or P-glycoprotein: Monitor for increased frequency and/or severity of ADRs from these substrates • Antimuscarinic drugs: Monitor for increased frequency or severity of anticholinergic ADRs
Use in specific populations	• Geriatric use: Recommended starting dose 50 mg/20 mg orally twice daily, consider a slower titration, max recommended dose 100 mg/20 mg twice daily • Renal impairment: not recommended in mod-to-severe renal impairment • Hepatic impairment: not recommended in mild hepatic impairment

Background

Schizophrenia is a severe, chronic psychiatric disorder affecting approximately 2.8 million adults in the United States and 23 million individuals globally, representing roughly 1% of the population.[2–5] Schizophrenia ranks as the third most common cause of disability among mental disorders, surpassed only by depressive (37.4%) and anxiety (22.9%) disorders. It also is frequently described as a leading cause of disability, specifically in young adults (ages ~20–45).[6] Patients with schizophrenia face a 15- to 20-year reduction in life expectancy, largely attributable to cardiovascular disease, metabolic complications from treatment, and high rates of suicide (lifetime risk approximately 5%–10%).[4,7–12]

Schizophrenia presents across three core symptom domains[7,13,14]:

- Positive symptoms: hallucinations, delusions, disorganized thinking and speech.
- Negative symptoms: flat affect, avolition, alogia, anhedonia, social withdrawal.
- Cognitive dysfunction: impaired working memory, attention, executive function.

Medication adherence is a major challenge. Approximately 74% of patients discontinue antipsychotics within 18 months, largely due to intolerable side effects including weight gain, metabolic syndrome, EPS, sedation, and hyperprolactinemia.[15] Treatment resistance is estimated in 20–30% of patients.[16–18] All currently approved antipsychotics (prior to Cobenfy) work primarily through antagonism of dopamine D2 receptors.

Current Standard of Care

The most recent comprehensive American Psychiatric Association Practice Guideline for Schizophrenia[19] predates Cobenfy's approval. It therefore does not directly address Cobenfy but establishes the framework within which it should be positioned:

- Recommends antipsychotic medication for all patients with schizophrenia experiencing an acute episode and for maintenance.
- Does not specify preferred agents for first-episode psychosis, emphasizing patient-centered selection based on efficacy and side effect profile.
- Recommends long-acting injectables for patients with history of poor adherence or patient preference.
- Recommends clozapine after ≥2 failed antipsychotic trials for treatment-resistant schizophrenia.
- Clozapine also is recommended for patients with substantial suicide risk or persistent aggression.

Unmet Needs

- Metabolic burden: Weight gain and dyslipidemia from second-generational antipsychotics significantly increase cardiovascular morbidity.
- EPS and tardive dyskinesia: Persistent concern, particularly with first-generation antipsychotics and high-dose second-generation antipsychotics.
- Negative and cognitive symptoms: Inadequately addressed by existing dopaminergic therapies.
- Treatment adherence: Side effect–driven discontinuation remains a primary barrier to long-term stability.
- Treatment resistance: 20%–30% of patients do not respond adequately to D2-blocking agents.

Pipeline

The schizophrenia treatment landscape is undergoing a mechanistic transformation, with multiple pipeline agents targeting pathways beyond traditional dopamine D2 receptor antagonism. Selected phase 3

investigational agents as of mid-2026 are summarized in the table below. Notably, Bristol-Myers Squibb also has an ongoing Phase I trial for a long-acting injectable formulation of Cobenfy. Key mechanistic categories in the schizophrenia pipeline include muscarinic receptor modulators (like Cobenfy), TAAR1/5-HT1A agonists, glutamate modulators, dopaminergic novel agents, and non-dopaminergic negative symptom agents.

Phase 3 Investigational Agents for Schizophrenia				
Agent	**Manufacturer**	**Mechanism of Action**	**Status**	**Key Notes**
NBI-1117568	Neurocrine Biosciences/ Nxera Pharma	Selective muscarinic M4 orthosteric agonist (non-dopaminergic)	Initiated April 2025	• Phase 2 met primary endpoint (PANSS −7.5 pts vs. placebo, effect size 0.61)[20] • Four ongoing Phase 3 studies[21–24]
Evenamide (NW-3509)	Newron Pharma	Voltage-gated sodium channel modulator → glutamate release inhibitor	2027	• ENIGMA-TRS 1 (n=600, 1-yr, 15/30 mg)[25] • ENIGMA-TRS 2 (n=400, 12-wk)[26] • Add-on for TRS patients failing ≥2 AAPs
LB-102 (N-methyl amisulpride)	LB Pharma	Selective D2/D3 and 5-HT7 receptor antagonist; methylated amisulpride derivative (improved BBB penetration)	2027–2028	• Phase 2 NOVA-1 met primary endpoint (PANSS reduction, ES 0.61 at 50 mg)[27] • Phase 3 NOVA-2 initiated March 2026[28] • Phase 3 NOVA-3[29] • Potential first-in-class benzamide AAP in US
MIN-101 Roluperidone	Minerva	5-HT2A serotonin receptor antagonist	2028	• Being investigated for negative symptoms • Received a CRL in 2024; working with FDA for a new phase 3 trial[30]

AAP = atypical antipsychotic; BBB= blood-brain barrier; CRL = Complete Response Letter; ES = effect size; PANSS = Positive and Negative Syndrome Scale (PANSS); TRS = treatment-resistant schizophrenia

Comparators on the Patients First Health Plan Formulary

Tier 1	olanzapine quetiapine fumarate risperidone
Tier 2	aripiprazole lurasidone [QL] olanzapine ODT quetiapine fumarate ER ziprasidone
Tier 3	asenapine [QL] Caplyta (lumateperone) [ST, PA, QL] paliperidone ER [QL] Rexulti (brexpiprazole) [QL] Vraylar (cariprazine) [QL]

Rationale

- The comparators for Cobenfy listed in the table are the generic and brand-name second-generation antipsychotics deemed to be the most cost-effective and used most commonly in meta-analyses and guidelines.
- Although clozapine is available on the formulary, it was intentionally not considered as a comparator to Cobenfy.
- Long-acting injectables were not considered because they are covered under the medical benefit for Patients First members.

Clinical Evidence Evaluation

Cobenfy has only been evaluated against placebo; no head-to-head studies currently exist. Comparative efficacy using systematic reviews and meta-analysis as well as guidelines and cost-effectiveness will be crucial for understanding its place in therapy.

Efficacy

FDA approval was based on the EMERGENT clinical program, comprising three placebo-controlled trials (EMERGENT-1, -2, -3) and two open-label long-term safety extensions (EMERGENT-4 and -5), all conducted in hospitalized adults with schizophrenia experiencing acute psychosis.[31–35] Patients were tapered off prior antipsychotics (89%) or were treatment-naive (11%) before a rapid 2-day inpatient titration. No patients had previously received clozapine.

All three EMERGENT trials met the primary and secondary endpoints.

Summary of Efficacy from the EMERGENT Pivotal Trials[31–33,36]

Study	N (mITT)	Cobenfy Δ in PANSS	Placebo Δ in PANSS	LSMD (95% CI); p-value	Secondary Endpoints
EMERGENT-1	182	−17.4 pts	−5.9 pts	−11.6 (−16.1, −7.1); p<0.0001 (d=0.75)	PANSS positive subscale, CGI-S
EMERGENT-2	252	−21.2 pts	−11.6 pts	−9.6 (−13.9, −5.2); p<0.0001 (d=0.61)	PANSS positive, negative, Marder negative factor, CGI-S
EMERGENT-3	256	−20.8 pts	−12.4 pts	−8.4 (−12.4, −4.3); p<0.0001 (d≈0.60)	PANSS positive, negative, Marder negative factor, CGI-S
Pooled EMERGENT 1–3	640	NR	NR	−9.9 (−12.4, −7.3); p<0.0001 (d=0.65)	PANSS subscales, CGI-S all significant; response onset at week 1

CGI-S = Clinical Global Impression-Severity; LSMD = least squares mean difference; mITT = modified intent-to-treat; NR = not reported; PANSS = Positive and Negative Syndrome Scale.

Comparative Effectiveness

Numerous systematic reviews and meta-analyses exist that describe comparative effectiveness in the absence of head-to-head studies. Hickey et al[37] had the most comprehensive analysis including a plethora of agents; however, limitations exist. To date, the review was presented as a poster only and remains unpublished. Further, clozapine was included as a comparator, which is not appropriate given its place in therapy for refractory patients. Fabiano et al[38] aligned with the ICER review in terms of agents included and results demonstrated.

ICER Network Meta-Analysis: ICER conducted a systematic review and network meta-analysis comparing xanomeline/trospium to three commonly used second-generation antipsychotics (olanzapine, risperidone, aripiprazole) across 33 trials (n = 7,193) to inform its health technology assessment.[39] All four active agents were more efficacious than placebo, but no statistically significant differences were found among the active treatments for PANSS total, positive, or negative symptom scores. All-cause discontinuation was highest for xanomeline/trospium vs comparators. Weight gain was lower with xanomeline/trospium than with olanzapine and risperidone. The ICER analysis concluded that xanomeline/trospium offers comparable efficacy to existing second-generation antipsychotics but was

priced above the cost-effectiveness threshold of $16,000–$20,000/year. Selected results from the ICER review are presented below.[39–41]

Table 3.2. Change from Baseline in PANSS Total Score

KarXT				
-1.4 (-7.64, 4.82)	Aripiprazole			
0.89 (-4.7, 6.48)	2.29 (-1.5, 6.12)	Olanzapine		
-1.73 (-7.63, 4.09)	-0.33 (-5.01, 4.31)	-2.63 (-6.29, 0.97)	Risperidone	
-9.78 (-14.83, -4.74)	**-8.38 (-12.04, -4.68)**	**-10.67 (-13.11, -8.24)**	**-8.05 (-10.99, -5.03)**	Placebo

Each box represents the estimated relative mean difference and 95% credible interval. Estimates in bold signify the 95% credible interval does not contain 0. Individual trial data can be found in Supplement Table D2.3.

Table 3.9. Evidence Ratings

Treatment	Comparator	Evidence Rating
KarXT	No antipsychotic therapy	P/I
KarXT	Aripiprazole	I
KarXT	Olanzapine	P/I
KarXT	Risperidone	P/I

I: insufficient, P/I: promising but inconclusive

Safety

- Serious adverse events with xanomeline/trospium were rare.[1,32,33,36,38,42,43]
- Discontinuation rates of xanomeline/trospium during the EMERGENT trials were similar to placebo (27.6% vs 22.7%) and were primarily driven by GI adverse events.[1,31–33]
- Unlike typical and atypical antipsychotics, xanomeline/trospium displayed minimal EPS (3.2%) and weight gain (5.9%).[1] Labeled adverse events and contraindications align with anti-muscarinic drugs, instead of antipsychotics.
- There are no long-term safety studies with xanomeline/trospium; however, we anticipate it would be similar to other anti-muscarinics.

Pooled EMERGENT Trials—Treatment-Emergent Adverse Events During the 5-Week Treatment Period[1,36,44]

Treatment-Related Adverse Events	Cobenfy (n=340) n (%)	Placebo (n=343) n (%)
Any	176 (51.8)	101 (29.4)
Serious	1 (0.3)	0 (0)
Most common*		
Nausea	58 (17.1)	11 (3.2)
Constipation	51 (15.0)	18 (5.2)
Dyspepsia	41 (12.1)	8 (2.3)
Vomiting	37 (10.9)	3 (0.9)

**Reported in >2% of people in the xanomeline/trospium group and at least twice the placebo rate.*

Economic Evidence Evaluation

Patients First evaluated a budget impact model from Bjerke et al[45] for a health plan with 1 million members. Projected spend and PMPM cost impact to Patients First members were adopted and are seen in the table below. One limitation to the Bjerke model is the health plan makeup is commercial Medicare and Medicaid versus our Patients First commercial-only plan.[45]

Budget Impact	Year 1	Year 2	Year 3
Projected spend[45]	$212,479	$658,881	$1,219,085
$ PMPM impact[45]	0.0177	0.0546	0.1006
Projected spend (extrapolated for Patients First)	$616,189	$1,910,754	$3,535,347

ICER Network Meta-Analysis: The ICER analysis concluded that xanomeline/trospium offers comparable efficacy to existing second-generation antipsychotics but was priced above the cost-effectiveness threshold of $16,000–$20,000/year.[39]

- Annual costs of generic comparators aripiprazole, risperidone, and olanzapine were $40, $62, and $150 per year, respectively.[46] ICER used a placeholder price of xanomeline/trospium of $20,000 which is close to its current price of $22,644 annually as of July 2026.[39]
- Per the ICER report, "Making the highly favorable assumption that KarXT [Cobenfy] does not increase the risk of metabolic syndrome and associated consequences beyond that seen in the general population, our analyses suggest that treatment with KarXT results in less time with diabetes and in greater QALYs, greater life years, and greater evLYs [equal-value life years]."[39]

Selected results from the ICER review are presented below. A sensitivity analysis was conducted, and researchers found the model was most sensitive to the 3-month metabolic syndrome probability.[39]

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Year Without Diabetes
KarXT*	$163,000	$347,000	$146,000	$60,000

evLY: equal-value life year, QALY: quality-adjusted life year

*Assuming a KarXT placeholder price of $20,000 per year.

Value Matrix and Recommendation

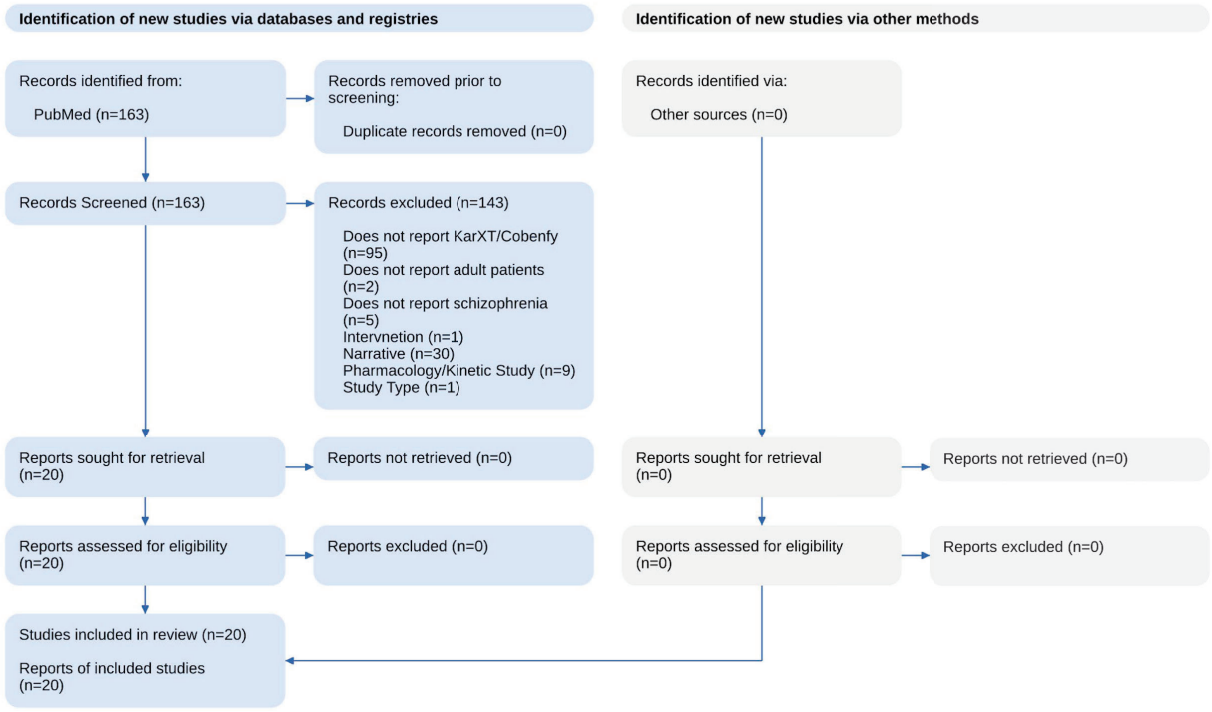
Domain	Finding	Rating
CLINICAL VALUE		
Net benefit: clinical efficacy vs comparator(s)	Based on systematic reviews, metanalysis, and indirect comparison, xanomeline/trospium offers comparable efficacy to existing second-generation antipyschotics.	Comparable (based on indirect evidence)
Safety profile	Unlike typical and atypical antipsychotics, xanomeline/trospium displayed minimal EPS (3.2%) and weight gain (5.9%). Labeled adverse events and contraindications align with antimuscarinic drugs, instead of antipsychotics. ADRs are similar to antimuscarinics.	Favorable
Place in therapy	Use after trial of 1-2 second generation atypical antipsychotics and/or ADRs from atypical antipsychotics are intolerable (i.e., EPS and metabolic effects)	
COST VALUE		
Cost vs comparator(s)	WAC of $22,664/year as of July 2026 representing a significant premium over generic second-generation antipsychotics (ranging from $40–$150 annually)[46]	High
Cost effectiveness	Per ICER[39], xanomeline/trospium was $163,000/QALY	Above threshold
Budget impact	Per Bjerke[45], estimated PMPM impact for Year 1 ($0.0177), Year 2 ($0.0546), Year 3 ($0.1006)	High
CONCLUSION AND RECOMMENDATION		
Overall Value Conclusion	While Cobenfy has a unique mechanism of action and minimal metabolic and EPS side effects, the efficacy is comparable to second generation antipsychotics; however, the cost is significantly higher, making the overall value low. Recommend implementation of utilization management tools.	Low value
Recommendation	May add to formulary Tier 3 ST, PA, QL Non-specialty/traditional	

Methodology

Databases Searched
PubMed, Clinicaltrials.gov, Cochrane

Search Strategy
((schizophrenia) AND ((xanomeline OR trospium chloride OR muscarinic agonists OR bladder antimuscarinics OR acetylcholine modulators OR cholinergic therapies) AND (efficacy OR safety OR clinical outcomes OR economic outcomes OR treatment impact))) AND "2020/01/01":"2026/01/31"[PDAT]

PRISMA



Traffic Light Diagram
See Appendix A: Traffic Light Diagram.

Secondary Sources
Drugs at FDA; FDA Adverse Events Monitoring System (previously FAERS); ClinicalTrials.gov; Commercial payer coverage criteria for competitor analysis; FDA Orange Book; Redbook; AMCP eDossier; AMCP/ISPOR Conference Proceedings; ICER.org.

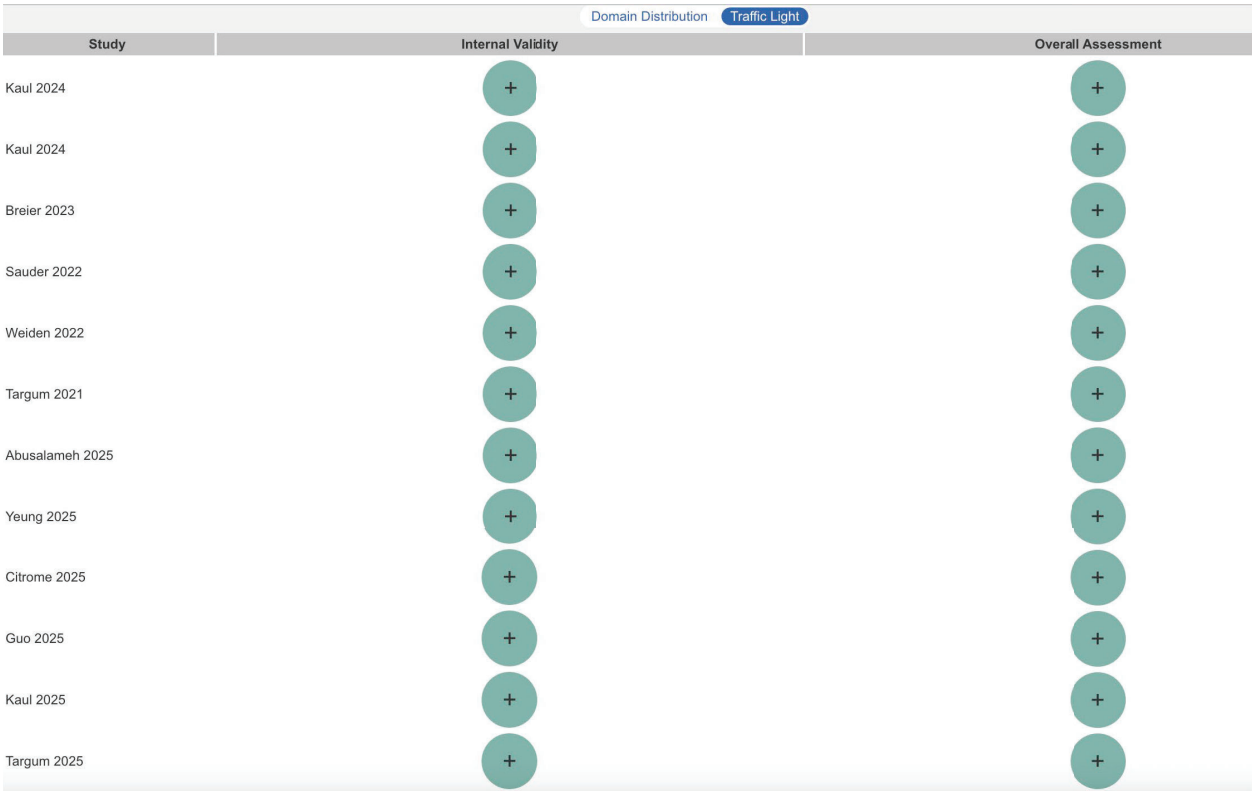
References

1. Cobenfy. Package insert. Bristol-Myers Squibb; 2026.
2. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: A Concise Overview of Incidence, Prevalence, and Mortality. *Epidemiol Rev*. 2008;30(1):67-76. doi:10.1093/epirev/mxn001
3. Saha S, Chant D, Welham J, McGrath J. A Systematic Review of the Prevalence of Schizophrenia. Hyman SE, ed. *PLoS Med*. 2005;2(5):e141. doi:10.1371/journal.pmed.0020141
4. World Health Organization (WHO). Schizophrenia. Updated October 6, 2025. Available at: https://www.who.int/news-room/fact-sheets/detail/schizophrenia Accessed August 4, 2026.
5. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr Bull*. 2018;44(6):1195-1203. doi:10.1093/schbul/sby058
6. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*. 2022;9(2):137-150. doi:10.1016/S2215-0366(21)00395-3
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Text Revision (DSM-5-TR), American Psychiatric Association, 2022.
8. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*. 2017;4(4):295-301. doi:10.1016/S2215-0366(17)30078-0
9. Laursen TM, Nordentoft M, Mortensen PB. Excess Early Mortality in Schizophrenia. *Annu Rev Clin Psychol*. 2014;10(1):425-448. doi:10.1146/annurev-clinpsy-032813-153657
10. Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature Mortality Among Adults With Schizophrenia in the United States. *JAMA Psychiatry*. 2015;72(12):1172. doi:10.1001/jamapsychiatry.2015.1737
11. Palmer BA, Pankratz VS, Bostwick JM. The Lifetime Risk of Suicide in Schizophrenia: A Reexamination. *Arch Gen Psychiatry*. 2005;62(3):247. doi:10.1001/archpsyc.62.3.247
12. Hor K, Taylor M. Review: Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol (Oxf)*. 2010;24(4_suppl):81-90. doi:10.1177/1359786810385490
13. Tandon R, Gaebel W, Barch DM, et al. Definition and description of schizophrenia in the DSM-5. *Schizophr Res*. 2013;150(1):3-10. doi:10.1016/j.schres.2013.05.028
14. Kahn RS, Keefe RSE. Schizophrenia Is a Cognitive Illness: Time for a Change in Focus. *JAMA Psychiatry*. 2013;70(10):1107. doi:10.1001/jamapsychiatry.2013.155
15. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. CATIE Investigators. *N Engl J Med*. 2005;353(12):1209-1223. doi:10.1056/NEJMoa051688
16. Howes OD, McCutcheon R, Agid O, et al. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry*. 2017;174(3):216-229. doi:10.1176/appi.ajp.2016.16050503
17. Siskind D, Orr S, Sinha S, et al. Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. *Br J Psychiatry*. 2022;220(3):115-120. doi:10.1192/bjp.2021.61
18. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988;45(9):789-796.
19. American Psychiatric Association. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia*. Third Edition. American Psychiatric Association Publishing; 2020. doi:10.1176/appi.books.9780890424841
20. A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-1117568 in Adults With Schizophrenia Who Warrant Inpatient Hospitalization. ClinicalTrials.gov identifier: NCT05545111. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT05545111.
21. A Global, Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of NBI-1117568 in Adults With Schizophrenia Who Warrant Inpatient Hospitalization. ClinicalTrials.gov identifier: NCT07105098. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT07105098.

22. A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of NBI-1117568 in Adults With Schizophrenia Who Warrant Inpatient Hospitalization. ClinicalTrials.gov identifier: NCT06963034. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT06963034.
23. A Phase 3, Multicenter, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Assess the Efficacy of NBI-1117568 in Preventing Relapse of the Symptoms of Schizophrenia and to Assess the Safety and Tolerability of NBI-1117568 in Adults With Schizophrenia. ClinicalTrials.gov identifier: NCT07227818. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT07227818.
24. A Global, Phase 3, Multicenter, Open-Label Study to Assess the Long-Term Safety and Tolerability of NBI-1117568 in Adults With Schizophrenia. ClinicalTrials.gov identifier: NCT07114874. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT07114874.
25. Study to Determine the Safety, Tolerability, and Efficacy of Evenamide in Patients With Chronic Schizophrenia (ENIGMA-TRS 1). ClinicalTrials.gov identifier: NCT04461119. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT04461119.
26. Evenamide, a Glutamate Release Modulator, as Add-On to Standard of Care in Subjects With Documented Treatment-Resistant Schizophrenia (ENIGMA-TRS 2). ClinicalTrials.gov identifier: NCT07184619. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT07184619.
27. A Randomized, Double-blinded, Placebo-controlled, Multicenter Study to Evaluate the Antipsychotic Efficacy and Safety of LB-102 in the Treatment of Adult Patients With Acute Schizophrenia (NOVA-1). ClinicalTrials.gov identifier: NCT06179108. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT06179108.
28. A Randomized, Double-blinded, Placebo-controlled, Multicenter Study to Evaluate the Antipsychotic Efficacy and Safety of LB 102 in the Treatment of Adult Patients With Acute Schizophrenia (NOVA-2). ClinicalTrials.gov identifier: NCT07363577. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT07363577.
29. A 52 Week, Open Label Safety and Tolerability Study of LB-102 in Adult Patients With Schizophrenia (NOVA-3). ClinicalTrials.gov identifier: NCT07369154. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT07369154.
30. A 12-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Monotherapy Study to Evaluate Efficacy of Roluperidone on Negative Symptoms in Adult Subjects With Schizophrenia, Followed by a 52-Week, Randomized, Double-Dummy Phase to Evaluate the Relapse Rate of Roluperidone and Antipsychotic Medications ClinicalTrials.gov identifier: NCT07565428. Accessed August 4, 2026. https://clinicaltrials.gov/study/NCT07565428.
31. Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A. Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia (EMERGENT-1). *N Engl J Med*. 2021;384(8):717-726. doi:10.1056/NEJMoa2017015
32. Kaul I, Sawchak S, Correll CU. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial. *Lancet*. 2024;403(10422):160-170. doi:10.1016/S0140-6736(23)02190-6
33. Kaul I, Sawchak S, Walling DP. Efficacy and Safety of Xanomeline-Trospium Chloride in Schizophrenia: A Randomized Clinical Trial (EMERGENT-3). *JAMA Psychiatry*. 2024;81(8):749-756. doi:10.1001/jamapsychiatry.2024.0785
34. An Extension Study to Assess Long-term Safety, Tolerability, and Efficacy of KarXT in Adult Patients With Schizophrenia (EMERGENT-4). October 28, 2024. https://clinicaltrials.gov/study/NCT04659174.
35. An Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of KarXT in Adult Patients With Schizophrenia (EMERGENT-5). September 17, 2025. https://clinicaltrials.gov/study/NCT04820309.
36. Kaul I, Sawchak S, Claxton A. Efficacy of xanomeline and trospium chloride in schizophrenia: pooled results from three 5-week, randomized, double-blind, placebo-controlled, EMERGENT trials. *Schizophrenia*. 2024;10(1). doi:10.1038/s41537-024-00525-6
37. Hickey C, Sidovar MF, Garcia A, et al. Network Meta-Analysis of the Efficacy, Safety, and Tolerability of Xanomeline plus Trospium Chloride Compared with Eight Atypical Oral Antipsychotics for the Acute Treatment of Schizophrenia. Social Science Research Network. Preprint posted online September 14, 2025:5420474. doi:10.2139/ssrn.5420474.
38. Fabiano N, Wong S, Zhou C, Correll CU, Højlund M, Solmi M. Efficacy, tolerability, and safety of xanomeline-trospium chloride for schizophrenia: a systematic review and meta-analysis. *Eur Neuropsychopharmacol*. 2025;92:62-73.

39. Tice JA, Whittington MD, McKenna A, Wright A, Richardson M, Pearson SD, Rind DM. KarXT for Schizophrenia: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, January 25, 2024. https://icer.org/assessment/schizophrenia-2024/#overview.
40. Wright AC, McKenna A, Tice JA, Rind DM, Agboola F. A network meta-analysis of KarXT and commonly used pharmacological interventions for schizophrenia. *Schizophr Res*. 2024;274:212-219. doi:10.1016/j.schres.2024.09.023
41. McKenna A, Tice JA, Whittington MD, et al. KarXT for schizophrenia–effectiveness and value: A summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council. *J Manag Care Spec Pharm*. 2024;30(6):624-628. doi:10.18553/jmcp.2024.30.6.624
42. Kaul I, Claxton A, Sawchak S. Safety and Tolerability of Xanomeline and Trospium Chloride in Schizophrenia. *J Clin Psychiatry*. 2025;86(1). doi:10.4088/jcp.24m15497
43. Antrim A. Trial Data Show Long-Term Safety, Efficacy of Xanomeline/Trospium for Schizophrenia. Pharmacy Times; May 4, 2025. Available at: https://www.pharmacytimes.com/view/trial-data-show-long-term-safety-efficacy-of-xanomeline-trospium-for-schizophrenia Accessed 8-3-2026.
44. Horan WP, Targum SD, Claxton A. Efficacy of KarXT on negative symptoms in acute schizophrenia: A post hoc analysis of pooled data from 3 trials. *Schizophr Res*. 2024;274:57-65. doi:10.1016/j.schres.2024.08.001
45. Bjerke A, Mantaian T, Gillard K, et al. Budget impact of xanomeline and trospium chloride for the treatment of adults with schizophrenia in the United States. *J Manag Care Spec Pharm*. 2026;32(4):458-469.
46. Redbook Online. IBM Micromedex [database online]. Truven Health Analytics/IBM Watson Health; 2020. Accessed July 24, 2026. https://www.micromedexsolutions.com.

Appendix A: Traffic Light Diagram



Appendix B: Coverage Criteria

Cobenfy is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist, indicated for the treatment of schizophrenia in adults.

Cobenfy will be considered for coverage under the pharmacy benefit for the indication listed above when the following criteria are met.

Initial Authorization

- Continuation of therapy: The patient is stable on Cobenfy for a minimum of 90 days.

—OR—

- The patient is 18 years of age or older.
- The patient has a diagnosis of schizophrenia.
- The patient has tried and failed or has a contraindication to two formulary atypical antipsychotics (e.g., risperidone, aripiprazole, quetiapine).
- The medication was prescribed by or in consultation with a psychiatrist.
- The patient has no FDA-labeled contraindications to the medication.

Non-FDA-approved uses are not approved.

Authorization expires in 1 year.

Quantity Limits

- The prescribed dose is consistent with FDA-approved package labeling (#60 per 30 days).

Reauthorization (annually)

- The patient's disease severity has improved and stabilized to warrant continued therapy.
- The patient has not experienced any treatment-restricting adverse effects (e.g. urinary retention, angioedema, increased heart rate).

References

1. Xanomeline/trospium oral capsules (Cobenfy). Product labeling. Bristol-Myers Squibb. January 2026.
2. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Schizophrenia Third Edition. Available at: https://psychiatryonline.org/doi/10.1176/appi.books.9780890424841.
3. Tice JA, Whittington MD, McKenna A, Wright A, Richardson M, Pearson SD, Rind DM. KarXT for Schizophrenia: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, January 25, 2024. https://icer.org/assessment/schizophrenia-2024/#overview.
4. Hickey C, Sidovar MF, Garcia A, et al. Network Meta-Analysis of the Efficacy, Safety, and Tolerability of Xanomeline plus Trospium Chloride Compared with Eight Atypical Oral Antipsychotics for the Acute Treatment of Schizophrenia. *Social Science Research Network*. Preprint posted online September 14, 2025:5420474. doi:10.2139/ssrn.5420474.
5. Fabiano N, Wong S, Zhou C, Correll CU, Højlund M, Solmi M. Efficacy, tolerability, and safety of xanomeline-trospium chloride for schizophrenia: A systematic review and meta-analysis. *Eur Neuropsychopharmacol*. 2025;92:62-73. doi:10.1016/j.euroneuro.2024.11.013.