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Drug Use Research & Management Program

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New Drug Evaluation: xanomeline/trospium

Date of P&T Review: February 6, 2025

Date of MHCAG Review: January 9, 2025

Generic Name: xanomeline/trospium chloride

End Date of Literature Search: 11/15/24

Brand Name (Manufacturer): COBENFY (Bristol-Myers Squibb Company)

Dossier Received: yes

Plain Language Summary:

- The Food and Drug Administration (FDA) recently approved a new medicine called xanomeline/trospium, that is taken twice a day by mouth, to decrease symptoms in people with schizophrenia. Schizophrenia is a mental health condition that affects how people think, feel and behave. Common symptoms of schizophrenia include hallucinations (seeing or hearing something that is not there), delusions (strong belief in something despite evidence that is not real) and thoughts that are not clearly ordered.
- Studies show that xanomeline/trospium decreases schizophrenia symptoms for people in the hospital. Studies have not evaluated:
 - Benefit or side effects beyond 5 weeks
 - Change in symptoms or side effects compared to other medicines
 - Return to work or school, or improvement in relationships with friends and family
 - Long-term symptom prevention, hospital visits, or death
- Studies show that xanomeline/trospium can have side effects including upset stomach, vomiting, diarrhea, and constipation. Studies did not include people who might have increased risk for these side effects. Because xanomeline/trospium may affect how well the liver works, the FDA recommends providers order labs to assess liver function before they prescribe this medicine.

Research Questions:

1. What is the evidence for efficacy of xanomeline/trospium for the treatment of schizophrenia and how does it compare to current therapy?
2. What is the evidence for safety of xanomeline/trospium in people with schizophrenia?
3. Are there subpopulations of adults (based on age, gender, race/ethnicity, disease duration or severity, or comorbid conditions) for whom xanomeline/trospium is more effective or associated with more harms?

Conclusions:

Efficacy

- There is low quality evidence that xanomeline/trospium improves symptoms in people with acute worsening of schizophrenia compared to placebo over 5 weeks. Evidence was downgraded for risk of bias and indirectness as trials were not conducted in an outpatient setting. In people with schizophrenia and without comorbid conditions, the average improvement on the Positive and Negative Syndrome Scale (PANSS) in 3 inpatient randomized controlled trials (RCTs) ranged from -21.6 to -17.4 points for xanomeline/trospium compared to -12.2 to -5.9 points with placebo (least square mean difference [LSMD] of -8.4 [95% CI -12.4 to -4.3] to -11.6 [95% CI -16.1 to -7.1]).¹⁻³ This improvement likely represents a clinically meaningful change in symptoms.⁴⁻⁷ In 2 inpatient trials, the Clinical Global Impression-Severity (CGI-S) score also improved compared to placebo (-1.2 vs. -0.7; LSMD -0.6 [95% CI -0.9 to -0.3]).^{1,3} The minimum clinically important difference in CGI-S is 1 point.
- There is insufficient data to evaluate long-term efficacy of xanomeline/trospium. Interim analyses of long-term extension studies indicate that over 50% of people prescribed xanomeline/trospium had discontinued treatment by 120 days.⁸ The primary reasons for discontinuation in extension studies included withdrawal of consent (18.7%), adverse events (14.9%), loss to follow-up (8.2%), and failure to adhere to protocol requirements (7.4%).⁸
- Studies did not evaluate quality of life, prevention of relapse, return to work and school, improvements in relationships with friends and family, hospital readmission, or mortality.
- There is no direct data to evaluate efficacy of xanomeline/trospium compared to other antipsychotics, and no data evaluating doses of 50/20mg twice daily as maintenance therapy.
- There is currently no data evaluating efficacy of xanomeline/trospium in combination with other antipsychotics. An ongoing trial is evaluating xanomeline/trospium as adjunct therapy with another antipsychotic for people with schizophrenia.⁹
- There is no data evaluating efficacy of xanomeline/trospium for conditions other than schizophrenia. There are ongoing phase 3 trials of xanomeline/trospium in Alzheimer's Disease psychosis.^{10,11}

Safety

- There are insufficient data to evaluate rates of serious adverse effects or discontinuation due to adverse effects with xanomeline/trospium compared to placebo. Data are significantly limited by inpatient setting, short-term treatment durations, and exclusion of populations with comorbid conditions which are common in patients with schizophrenia.¹⁻³
- Xanomeline/trospium was associated with significant rates of gastrointestinal (GI) adverse events compared to placebo in short-term trials (e.g., nausea, vomiting, dyspepsia, constipation, diarrhea, abdominal pain, and reflux disease).¹⁻³
- There are insufficient data to evaluate long-term safety or adverse effects of xanomeline/trospium. Short-term trials did not identify an association with akathisia or weight gain, but long-term studies are needed to confirm these findings.
- Xanomeline/trospium is contraindicated in people with urinary retention, moderate to severe hepatic impairment, gastric retention, or untreated narrow-angle glaucoma.¹² Other warnings and precautions include risk for angioedema, biliary disease, decreased gastric motility, increased heart rate, anticholinergic side effects, and central nervous system effects (e.g., dizziness, confusion, hallucinations, and sedation).¹² Labeling recommends liver function tests prior to starting treatment and periodically as needed to monitor for liver injury and biliary disease.¹²
- There are no data evaluating adverse effects of xanomeline/trospium compared to other antipsychotics or evaluating safety with concomitant antipsychotic use. People who were prescribed concomitant mental health drugs were excluded from clinical trials, but there is potential for increased rates of adverse events when used in combination with common antidepressants.

Subgroups

- There are insufficient data to evaluate efficacy of xanomeline/trospium for in children or patients over 65 years of age. Most patients enrolled in clinical trials identified as Black or White and other races were under-represented.¹² Post-hoc analyses based on age, sex, and race did not identify any differences in efficacy.⁸ Most patients included in phase 3 clinical trials had prior experience with antipsychotics, but were not considered to have treatment resistant schizophrenia.^{2,3}
- There are insufficient data to evaluate differences in safety for subpopulations. People prescribed concomitant mental health drugs and comorbidities that may increase risk for adverse events were excluded from clinical trials.¹⁻³ Based on metabolism of xanomeline/trospium, inhibitors of CYP2D6 (such as bupropion, fluoxetine, paroxetine, or duloxetine) may increase exposure to xanomeline and risk of adverse events.¹² People with comorbid conditions or elderly may be at increased risk of anticholinergic adverse events from xanomeline/trospium, but these populations were excluded from clinical trials limiting ability to make evidence-based conclusions.⁸
- The Oregon Mental Health Clinical Advisory Group (MHCAG) reviewed evidence for xanomeline/trospium in January 2025. Members expressed concerns about the lack of safety or efficacy data with other mental health medications particularly antipsychotics and antidepressants with potential drug interactions with xanomeline/trospium. The MHCAG recommended implementation of a safety edit designed to mitigate those specific concerns.

Recommendations:

- Maintain xanomeline/trospium as voluntary non-preferred on the Preferred Drug List (PDL).
- Implement prior authorization criteria to promote safe use of xanomeline-trospium with other antipsychotics or antidepressants (**Appendix 2**).

Background:

Schizophrenia is a severe mental health disorder characterized by presence of positive symptoms (delusions, hallucinations, disorganized speech, thought and behavior), negative symptoms (blunted affect, lack of speech or social interactions, anhedonia, and decreased motivation), and cognitive symptoms (impaired executive function, attention, and memory).¹³ Diagnosis based on the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) criteria requires presence of 1) at least one positive symptom with 2 or more total symptoms characteristic of schizophrenia and 2) social or occupational disruption in work, relationships, or self-care.¹⁴ Symptoms and social dysfunction generally persist for at least 6 months in the absence of alternative medical causes.¹⁴ About 0.6 to 1.9% of people in the United States are estimated to have schizophrenia.¹⁴ The prevalence of schizophrenia based on gender, race and ethnicity may vary. Diagnosis of schizophrenia may be 3-5-times more common in Black and Hispanic populations compared to white populations and more common in males than females.^{13,14} However, data also shows there may be an increased risk for misdiagnoses of psychiatric conditions in non-white populations.¹⁴ Onset of schizophrenia symptoms occurs most commonly in early adulthood and can have a significant impact on quality of life, social relationships, and occupational status. Less than 20% of patients who experience first-episode psychosis will remain relapse-free over their lifetime, and at least one-third of patients continue to have symptoms despite treatment.¹⁴ Factors associated with worse prognosis and disease course include presence of negative symptoms, longer duration of untreated psychosis, slow symptom onset, and symptom presentation at an earlier age.¹⁴ Schizophrenia has been associated with increased risk of overall mortality, mortality due to suicide, substance use disorders, cognitive impairment, and chronic medical conditions (e.g., diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease).¹⁴

Antipsychotic medications are the primary treatment recommended for schizophrenia. Medication selection is dependent on risks for adverse effects, patient preferences, prior treatment response, and availability of a long-acting formulation.¹⁵ All antipsychotic medications are associated with adverse effects that limit medication tolerability and contribute to treatment discontinuation. Adverse effects related to antipsychotic use include sedation, metabolic (e.g, weight gain, diabetes, hypertension, dyslipidemia), cardiovascular (e.g., QT prolongation), hormonal (e.g, elevated prolactin levels, sexual dysfunction), and movement

disorders (e.g., akathisia, dyskinesias, dystonia, parkinsonism).^{13,14} Antipsychotics with long-acting formulations include aripiprazole, risperidone, paliperidone, fluphenazine, and haloperidol. The Oregon Mental Health Clinical Advisory Group recommends that providers consider use of these specific medications because long-acting injectable antipsychotics have shown lower risk of hospitalization and relapse when compared to oral antipsychotics.¹⁵ Clozapine is usually recommended for people who have had inadequate response to more than 2 antipsychotics.¹⁵ Non-pharmacological therapy including psychological counseling, skills training, psychoeducation, or cognitive therapy is also usually recommended in conjunction with pharmacological therapy.

Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales. The Clinical Global Impression Scale (CGI) evaluates disease severity and improvement using a 7-point analogue scale with lower scores indicating less severe symptoms and a change of 1 point corresponding to a minimum clinically important difference (MCID).¹⁶ The Positive and Negative Syndrome Scale (PANSS) evaluates 30 items in patients with schizophrenia. Each item is scored on a 7-point scale, with lower scores indicating less severe symptoms (range 30-210).¹⁶ This scale can also be subdivided to assess general psychopathology (16 items), positive symptoms (7 items), or negative symptoms (7 items). The 7 negative symptom questions are also commonly referred to as the Marder negative factor score.¹⁷ There is no established MCID for the PANSS, though improvements of 16-34% have been correlated to 1 point improvements in CGI-S,^{4,5} 4-8 points have been correlated to increases in employment⁷ and improvements of 10 points have been correlated with reduced hospitalization.⁶ Response to treatment is typically defined in most clinical trials as greater than 20% improvement in the PANSS score.

In the Oregon Health Plan (OHP), antipsychotics are exempt from traditional PDL requirements. However, clinical prior authorization (PA) criteria that address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use for sleep and for antipsychotic prescribing in children 6 years of age or younger. Injectable formulations of paliperidone, aripiprazole, risperidone, haloperidol and fluphenazine are on the PDL. However, most antipsychotic use in the OHP is for oral second-generation antipsychotics including aripiprazole, quetiapine, risperidone, and olanzapine.

Most antipsychotic drugs have activity at dopaminergic D2 receptors. However, xanomeline is a new oral antipsychotic medication which has activity at muscarinic (cholinergic), receptors instead of dopaminergic D2 receptors. Xanomeline is administered in combination with trospium, an oral anticholinergic drug with activity primarily in the peripheral tissues and limited ability to cross the blood brain barrier. The combination allows for cholinergic effects in the central nervous system with reduced adverse cholinergic effects in peripheral tissue. Adverse effects generally associated with cholinergic drugs include nausea, vomiting, diarrhea, gastroesophageal reflux disease, pupil constriction, bronchospasm, bradycardia, urination, lacrimation, sweating, salivation, and somnolence. Anticholinergic drugs often cause adverse effects related to dyspepsia, constipation, urinary retention, dry mouth, dry eye, and headache. Notably, trospium is contraindicated in patients with (or at risk for) urinary retention, gastric retention, and untreated narrow-angle glaucoma. The combination of xanomeline/trospium was primarily studied in short-term, inpatient trials with only limited data on adverse effects from non-comparative long-term extension studies. It is dosed twice daily.

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

FDA approval of xanomeline/trospium was primarily based on 2 phase 3 trials with supporting data from one phase 2 trial and interim analysis of 2 extension studies. Double-blind, placebo-controlled RCTs were conducted in an inpatient setting over 5 weeks and evaluated change in total PANSS score from baseline.¹⁻³ Xanomeline/trospium was dosed at 50/20 mg twice daily for 2 days, then 100/20 mg twice daily for 7 days at least 2 hours. Based on tolerability and response,

dose could be further titrated to 125/30 mg twice daily.¹⁻³ Administration is recommended at least 1 hour before or 2 hours after a meal as pharmacokinetic studies have identified food may increase absorption of xanomeline.¹² In EMERGENT-2, over 90% of patients in phase 3 trials were titrated to 125/30 mg twice daily and few patients (6%) had dose reductions due to adverse events.³

Adults enrolled in these trials had an acute exacerbation or relapse, moderate symptoms of schizophrenia (PANSS score 80-120 and a CGI-S score >4), and moderate-severity in at least 2 positive symptoms of schizophrenia (e.g., delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution).¹⁻³ People were excluded if they had comorbid physical or mental health conditions, were prescribed other mental health drugs, had unstable living situations, or had more severe symptoms (e.g., risk for suicidal behavior, recent hospitalizations for >30 days, violent or destructive behavior, or involuntary hospitalization).¹⁻³ Enrolled patients had a mean PANSS score at baseline of 97-98 points, and a mean CGI-S score of 5.¹⁻³ Most patients had been on antipsychotic therapy sometime in the 6 months before study enrollment, but patients were not treatment-resistant.⁸ Enrolled patients were required to have discontinued all other antipsychotics within 5 half-lives for oral products or 12 weeks for injectable products (24 weeks for INVEGA TRINZA).³ Studies generally had high or unclear risk for performance and attrition bias. Attrition was more than 20% for all studies and treatment-emergent GI side effects increased risk for functional unblinding of providers and patients.¹⁻³

Compared to placebo, xanomeline/trospium improved acute schizophrenia symptoms as evaluated by the PANSS at 5 weeks in all 3 RCTs. The average improvement in the PANSS for people treated with xanomeline/trospium was 21.6, 20.6 and 17.4 points in each trial compared to people who received placebo (11.6, 12.2, 5.9 points) corresponding to LSMD of -9.6 (95% CI -13.9 to -5.2), LSMD of -8.4 (95% CI -12.4 to -4.3), and LSMD of -11.6 (95% CI -16.1 to -7.1), for each trial, respectively.¹⁻³ While about half of symptom improvement may be attributable to a placebo response, these changes likely represent clinically meaningful changes in symptoms. Improvements in PANSS of 16-34% has been correlated to 1-point improvements in CGI-S,^{4,5} 4-8 points have been correlated to increases in employment⁷ and improvements of 10 points have been correlated with reduced hospitalization.⁶ Symptom improvement was apparent at the first evaluation time point (after 2 weeks of therapy) and continued to improve over the 5-week study duration.¹⁻³ Secondary endpoints included changes in PANSS subscales (positive symptoms, negative symptoms, Marder negative factor) and CGI-S scores. The PANSS positive symptom subscale was consistent with the primary endpoint for all 3 trials.¹⁻³ Two trials also showed improvement in negative symptom subscales and CGI-S severity scores with xanomeline/trospium compared to placebo.^{1,3} In one RCT, there was no difference between placebo and xanomeline/trospium in negative symptom subscales.² However, studies primarily enrolled patients with acute exacerbations of schizophrenia who had positive symptoms, and studies were not powered to evaluate differences in negative symptoms. Most patients in the clinical trials were male (70%) and identified as Black or White.⁸ The average age of enrolled patients was 46, 43, 42 years in each trial. Evaluation of subgroups did not show differences in efficacy of xanomeline/trospium based on age, sex or race.¹²

Applicability to the OHP population is limited by extensive exclusion criteria. People with comorbid physical or mental conditions and people on concomitant mental health drugs were excluded from clinical trials. The efficacy of xanomeline/trospium in combination with antidopaminergic antipsychotics or other mental health drugs is currently unknown, and there is no direct comparative evidence of xanomeline/trospium versus antidopaminergic antipsychotics for treatment of schizophrenia. One ongoing trial (with estimated completion in 2025) is evaluating xanomeline/trospium as adjunct therapy with another antipsychotic for people with schizophrenia and insufficient response to at least one prior antipsychotic therapy.⁹ Data from available RCTs demonstrates improvement in overall symptom severity and positive symptoms for adults hospitalized with schizophrenia. The impact on negative symptoms is less clear, and trials have not evaluated other outcomes such as quality of life, activities of daily living, return to work, disability, or mortality. Symptoms of schizophrenia continued to improve compared to placebo over the 5-week trial period, but the only available data on long-term efficacy beyond 5 weeks is from open-label, non-comparative extension trials.

While some antipsychotics have mental health indications outside schizophrenia, there is currently no evidence to support xanomeline/trospium for any indication other than schizophrenia. Ongoing studies are evaluating use of xanomeline/trospium in people with psychosis related to Alzheimer’s disease.^{10,11}

Clinical Safety:

At the time of FDA review, 1,594 people had been exposed to treatment with xanomeline/trospium: 347 with treatment longer than 6 months and 150 with treatment for more than 1 year.¹² Data were primarily based on the 2 inpatient, phase 3, placebo-controlled studies including 504 adults and interim analyses of 2 long-term extension studies in the outpatient setting.¹² During inpatient clinical trials, discontinuations due to adverse events occurred in 6% of patients treated with xanomeline/trospium compared to 4% of patients treated with placebo.¹² Of 718 patients who were enrolled in the long-term studies, 53% discontinued treatment by 120 days.⁸ The primary reasons for discontinuation in extension studies included withdrawal of consent (18.7%), adverse events (14.9%), loss to follow-up (8.2%), and failure to adhere to protocol requirements (7.4%).⁸ Gastrointestinal events were generally mild, but were the most common type of event leading to treatment discontinuation.¹² Post-hoc analyses did not identify a dose response for common adverse events between 100/20 mg and 125/30 mg doses indicating that dose adjustment may not improve tolerability.⁸ However, in clinical trials, dose was titrated based on tolerability, and studies were not designed to detect differences between doses. Serious adverse events were infrequently reported. Four deaths occurred during the clinical trial program, all in people randomized to xanomeline/trospium.⁸ All deaths occurred more than 1 week after the last reported dose of the medication; cause of death was methamphetamine abuse in 2 cases and the cause was unknown in 2 cases.⁸

The most common type of adverse events reported in 5-week phase 3 trials were GI events (**Table 1**).¹² The rate of adverse GI effects generally improved over time. Treatment with xanomeline/trospium was also associated with hypertension, tachycardia, and dizziness.¹² Increases in heart rate were observed in both phase 3 trials and in a dedicated 8-week clinical study evaluating 24-hour ambulatory blood pressure in people receiving xanomeline/trospium. On average, heart rate was increased by 9.8 beats per minute (bpm) (95% CI 7.5 to 12.2) after 8 weeks of treatment.^{8,12} Similar increases were observed in phase 3 studies after 5 weeks of treatment (11.4 bpm with xanomeline/trospium compared to 5.5 bpm with placebo).¹² Heart rate monitoring is recommended before treatment and as clinically indicated during therapy. Other adverse effects which occurred less frequently with xanomeline/trospium but were more common than placebo included dry mouth, blurred vision, somnolence, orthostatic hypotension, extrapyramidal symptoms, salivary hypersecretion, and cough. In long-term extension studies, 38% of people experienced at least one cholinergic adverse event and 36% experienced at least one anticholinergic adverse event.⁸ Notably, symptoms of akathisia were similar between xanomeline/trospium in phase 3 RCTs (2.1% vs. 0.9%) with similar rates in the long-term extension studies (1.8% and 1.3%).⁸ In short-term phase 3 RCTs, xanomeline/trospium was not associated with metabolic adverse events (e.g., weight changes, dyslipidemia, hyperglycemia, metabolic syndrome) compared to placebo (2.9% vs. 2.0%).⁸ In longer-term extension studies, the proportion of people who had at least one metabolic related adverse event was 13.5%, and 65% of patients had a reduction in body weight from baseline (average change from baseline of -2 kg).⁸ Longer-term studies are need to confirm incidence of these adverse events.

Table 1. Adverse events reported in phase 3 trials occurring in ≥5% of patients and more common than placebo¹²

	Xanomeline/trospium (n=251)	Placebo (n=253)	Difference
Gastrointestinal			
Nausea	19%	4%	15%
Dyspepsia	18%	5%	13%
Constipation	17%	7%	10%
Vomiting	15%	1%	14%

Abdominal pain	8%	4%	4%
Diarrhea	6%	2%	4%
Gastroesophageal reflux disease	5%	1%	4%
Other			
Hypertension	11%	2%	9%
Tachycardia	5%	2%	3%
Dizziness	5%	2%	3%

Xanomeline/trospium is contraindicated in people with urinary retention, moderate or severe renal impairment (estimated glomerular filtration rate < 60 mL/min), moderate-severe hepatic impairment (Child-Pugh Class B or C), gastric retention, or untreated narrow-angle glaucoma. Individuals any of these conditions may be at increased risk of adverse events with xanomeline/trospium. Xanomeline is metabolized in the liver and hepatic impairment may increase exposure of xanomeline. Additionally, xanomeline/trospium was associated with transient increases in liver enzymes in clinical trials which appear to be consistent with cholinergic effects on the gallbladder and biliary system. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) more than 3-times the upper limit of normal occurred for 2.8% of patients treated with xanomeline/trospium compared to 0.4% of patients treated with placebo.¹² Liver function tests are recommended prior to treatment and as clinically indicated with presence of GI symptoms which may be related to gallbladder, pancreatic, or biliary disorders. Because trospium is excreted through the kidneys, renal impairment may increase risk of anticholinergic adverse reactions including dry mouth, constipation, dyspepsia, urinary tract infections and urinary retention. In open-label extension studies, urinary retention was reported in 3.5% of patients who received xanomeline/trospium, and was more common in males, geriatric patients and people with pre-existing risk factors.¹² Urinary tract infections were reported for 2.3% of patients who received xanomeline/trospium and were more common in females.¹² Clinical trials excluded patients older than 65 years of age. However, caution is generally recommended with use of anticholinergic medications in older patients because of increased risk for urinary retention and renal impairment. The FDA label also includes precautions for people with ulcerative colitis, intestinal atony, and myasthenia gravis as these conditions may increase risk of gastric retention.

Required post-marketing trials include a pregnancy exposure registry for patients exposed to xanomeline/trospium during pregnancy. Safety of xanomeline/trospium has not been evaluated during pregnancy, and there are no data on presence of xanomeline in human milk. However, in animal studies, xanomeline was associated with maternal and fetal toxicities (such as growth suppression, early abortion, decreased fetal weight, decreased fetal viability, and neonatal death).¹² Xanomeline and trospium were also present in milk during animal lactation studies.¹² Untreated schizophrenia has been associated with adverse perinatal and maternal outcomes (e.g., preterm birth, relapse, hospitalization, suicide), so providers should evaluate potential risks and benefit when considering use of xanomeline/trospium for pregnant or breastfeeding patients.¹²

Patients with co-occurring mental health disorders and patients prescribed concomitant mental health drugs were excluded from clinical trials. If xanomeline/trospium is being considered in these patients, providers should be aware of potential drug interactions which have the potential to increase risk for adverse events:¹²

- CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, duloxetine, etc.) increase xanomeline concentrations. Because of known variations in genetic coding for CYP2D6, xanomeline exposure is higher (median 15% increase in AUC₀₋₁₂) for CYP2D6 intermediate metabolizers and lower (by a median of 43%) for ultra-rapid metabolizers.

- Xanomeline transiently inhibits CYP3A4 and p-glycoprotein in the intestine so it may increase concentrations for substrates of p-glycoprotein or CYP3A4 (e.g., alprazolam, carbamazepine, midazolam, simvastatin, triazolam, etc.).
- Additive effects for drugs with anticholinergic side effects (e.g., clozapine, quetiapine, olanzapine, tricyclic antidepressants, etc.).

Evidence Gaps

Clinical trials of xanomeline/trospium had extensive exclusion criteria which limits evidence for people with comorbid conditions and people prescribed concomitant medications. Drug interactions with CYP2D6 inhibitors (including common antidepressants) have the potential to increase risk for cholinergic adverse events, but people prescribed these drugs were excluded from clinical trials. Trials occurred in the inpatient setting and were generally of short duration (5 weeks) with only limited data from longer-term extension studies. Attrition was generally high (>20%) for a short-term, inpatient trial, and discontinuation related to adverse events may be higher in an outpatient setting. In long-term extension studies, 53% of people had discontinued treatment by 120 days, but the lack of a comparator group makes it difficult to determine if the long-term discontinuation rate would be any different compared to placebo. Development of adverse effects such as movement and metabolic disorders with longer-term use is unknown. However, metabolic and movement disorders are not a common adverse event associated with other cholinergic or anticholinergic drugs. In short-term studies phase 3 trials, extrapyramidal symptoms (e.g., dyskinesia, dystonia, drooling, muscle contractions/spasms) were slightly more common in patients treated with xanomeline/trospium compared to placebo (2% vs. <1%) while incidence of akathisia and metabolic parameters was low and similar between groups.¹² Pediatric patients and patients older than 65 years of age were also excluded from clinical trials.¹² Trials primarily enrolled people identifying as White or Black and other populations were under-represented. There are no data directly comparing adverse effects of xanomeline/trospium to antipsychotics, the current standard of care for people with schizophrenia. Data on the safety of xanomeline/trospium in other conditions is currently insufficient.

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Psychosis symptoms (e.g., PANSS, CGI-S)
- 2) Quality of life, work/school engagement, activities of daily living, or disability
- 3) Hospitalization or emergency department utilization
- 4) Mortality
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Improvement in PANSS total symptom score

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Kaul, et al. 2024. ³ EMERGENT-2 NCT04659161	1. xanomeline/ trospium orally twice daily* 2. placebo	<u>Demographics:</u> - Male 75% - Age: 45.9 (SD 10.6) years - Race: Black or African American: 75% White: 23% - Mean PANSS (SD) total: 98.1 (SD 9.2)	<u>ITT:</u> 1. 126 2. 126 <u>mITT:</u> (had post-baseline PANSS)	<u>Primary Endpoint:</u> Change in PANSS after 5 weeks 1. -21.2 (SE 1.7) 2. -11.6 (SE 1.6) LSMD -9.6 (95% CI -13.9 to -5.2); p<0.0001	NA	<u>DC due to AE:</u> 1. 10 (8%) 2. 6 (5%) <u>Serious AE:</u> 1. 2 (2%)	NA for all	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> Low. Computer generated randomization with allocation concealment for patients and investigators. Baseline demographics were balanced between groups and between ITT and mITT populations. <u>Performance Bias:</u> High. Blinded with use of matching placebo identical in size, shape, color and appearance. Adverse GI events increased risk of functional unblinding.

<p>PC, DB, MC, inpatient, phase 3 RCT</p>	<p>*Initial dose: 50/20 mg twice daily for 2 days, then 100/20 mg twice daily for 7 days. After 1 week, dose could be titrated to 125/30 mg twice daily based on tolerability and response.</p> <p>5 weeks</p>	<p>positive: 26.7 (SD 3.9) negative: 22.9 (SD 3.9) Marder negative factor: 22.7 (SD 4.9) - CGI-S: mean 5.1 (SD 0.6)</p> <p><u>Key Inclusion Criteria:</u> - Age: 18-65 years - Schizophrenia diagnosis - PANSS 80-120 and score >4 (moderate symptoms) on ≥2 positive symptom items (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution) - CGI-S ≥ 4 (moderately ill) - Acute exacerbation requiring hospitalization within prior 2 months - Willing to stay in an inpatient setting for the study duration (5 weeks) - Stable living situation and anticipated to return there after discharge</p> <p><u>Key Exclusion Criteria:</u> - First episode or newly diagnosed schizophrenia - Comorbid mental health diagnoses including mild SUD - Risk for suicidal behavior (confirmed by C-SSRS with ideation in prior 2 months or behavior within prior 12 months) - Psychiatric hospitalization for >30 days in 90 days before screening - Risk of violent or destructive behavior or involuntary hospitalization - Lithium, other antipsychotics, TCA, SSRIs, anticonvulsants, MAOIs (as-needed anxiolytics permitted) - PANSS improvement >20% between screening and baseline - Clinically significant comorbid conditions of any of the following: CV, pulmonary, hepatic, renal</p>	<p>1. 117 2. 119</p> <p><u>PP:</u> 1. 94 2. 100</p> <p><u>Attrition:</u> 1. 32 (25%) 2. 26 (21%)</p>	<p><u>Secondary Endpoints (change after 5 weeks)</u> PANSS positive subscale 1. -6.8 (SE 0.5) 2. -3.9 (SE 0.5) LSMD -2.9 (95% CI -4.3 to -1.5); p<0.0001</p> <p>PANSS negative subscale 1. -3.4 (SE 0.5) 2. -1.6 (SE 0.5) LSMD -1.8 (95% CI -3.1 to -0.5); p=0.0055</p> <p>PANSS Marder negative factor score 1. -4.2 (SE 0.5) 2. -2.0 (SE 0.5) LSMD -2.2 (95% CI -3.6 to -0.8); p=0.0022</p> <p>CGI-S scale 1. -1.2 (SE 0.1) 2. -0.7 (SE 0.1) LSMD -0.6 (95% CI -0.9 to -0.3); p<0.0001</p> <p>PANSS responders (≥30% improvement) 1. 51/93 (55%) 2. 28/99 (28%) PP Difference: 27% (95% CI 13 to 39); p<0.0001</p>	<p>27%/4</p>	<p>2. 2 (2%)</p> <p><u>HTN:</u> 1. 12 (10%) 2. 1 (1%)</p> <p><u>Change in heart rate (day 28):</u> 1. 11.6 bpm (SD 13.86) 2. 2.4 bpm (SD 12.75)</p> <p><u>Treatment-emergent AE (mostly GI):</u> 1. 95 (75%) 2. 73 (58%)</p>	<p><u>Detection Bias:</u> High. Data assessors blinded, but adverse GI events increased risk of unblinding.</p> <p><u>Attrition Bias:</u> High. Attrition was balanced between groups but high for a short-term, inpatient study. Mixed model for repeated measures analysis used and missing values were assumed to be missing at random and handled using a likelihood-based modeling approach.⁸ Sensitivity analyses evaluating the impact of missing data on the primary outcome demonstrated similar direction of effect.⁸ Pre-specified hierarchical testing plan was used to control for type 1 error.</p> <p><u>Reporting Bias:</u> Low. Most outcomes were reported as pre-specified. PANSS responders with a ≥30% improvement in PANSS score were reported as a proportion of people who completed 5 weeks of treatment.</p> <p><u>Other Bias:</u> Low. Study sponsor was involved in trial design, data interpretation, and manuscript preparation. A contracted entity was responsible for data collection and analyses.</p> <p>Applicability: <u>Patient:</u> n=407 screened, n=252 randomized. The most common reasons for exclusion were abnormal lab values or physical findings (65%), and medical or psychiatric history (30%). Patients with comorbid physical or mental health conditions were excluded, and safety/efficacy in combination with common mental health drugs is unclear. Patients with less severe symptoms (PANSS <80) and more severe symptoms (risk for suicide, violent behavior, or prior hospitalizations > 30 days) were excluded. Study included a significant proportion of people who identified as Black, African American or White; other races/ethnicities were under-represented. Studies were conducted in an inpatient setting limiting applicability in an outpatient setting.</p> <p><u>Intervention:</u> Dosing is consistent with the FDA-approved labeling. Dose was selected based on phase 1 trials demonstrating antipsychotic efficacy at 225 mg/day and studies showing 200mg of xanomeline combined with trospium had comparable pharmacokinetics.¹</p> <p><u>Comparator:</u> Placebo appropriate to determine efficacy. No comparison to current standard of care (antipsychotics) which would help determine place in therapy.</p>
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		<p>hematologic, GI, endocrine, immunologic, dermatologic, neurologic, oncologic, HIV, biliary duct</p> <ul style="list-style-type: none"> - Clinically significant laboratory or ECG abnormalities - History or high risk for urinary retention, gastric retention or narrow-angle glaucoma - History of IBS or treatment for constipation 						<p>Outcomes: PANSS is a well-established measure to assess symptoms of schizophrenia in clinical trials. The change in PANSS associated with treatment likely correlates with a MCID with more responders to treatment compared to placebo. Symptoms continued to improve through 5 weeks, but long-term outcomes are unknown. Inpatient stays of 5 weeks are not typical in clinical practice for people with moderate symptoms.</p> <p>Setting: 22 inpatient sites in the U.S. from December 2020 to April 2022.</p>
<p>2. Kaul, et al. 2024.²</p> <p>EMERGENT-3 NCT04738123</p> <p>PC, DB, MC, inpatient, phase 3 RCT</p>	<p>1. xanomeline/trospium orally twice daily*</p> <p>2. placebo</p> <p>Dosing: See EMERGENT-2</p> <p>5 weeks</p>	<p>Demographics:</p> <ul style="list-style-type: none"> - Male 74.6% - Age: 43 years (SD 11.8) - Race: White: 38% Black or African American: 61% - Mean PANSS (SD) total: 97.0 (SD 8.9) positive: 26.7 (SD 3.5) negative: 22.3 (SD 3.5) Marder negative factor: 21.9 (SD 3.9) - CGI-S: mean 5.1 (SD 0.6) <p>Key Inclusion Criteria: See NCT04659161/EMERGENT-2</p> <p>Key Exclusion Criteria: See NCT04659161/EMERGENT-2</p>	<p>ITT:</p> <ol style="list-style-type: none"> 125 131 <p>mITT: (had post-baseline PANSS)</p> <ol style="list-style-type: none"> 114 120 <p>PP:</p> <ol style="list-style-type: none"> 79 93 <p>Attrition:</p> <ol style="list-style-type: none"> 46 (37%) 38 (29%) 	<p>Primary Endpoint: Change in PANSS after 5 weeks</p> <ol style="list-style-type: none"> -20.6 (SE 1.6) -12.2 (SE 1.6) <p>LSMD -8.4 (95% CI -12.4 to -4.3); p<0.001</p> <p>Secondary Endpoints (change after 5 weeks)</p> <p>PANSS positive subscale</p> <ol style="list-style-type: none"> -7.1 (SE 0.5) -3.6 (SE 0.5) <p>LSMD -3.5 (95% CI -4.7 to -2.2); p<0.001</p> <p>PANSS negative subscale</p> <ol style="list-style-type: none"> -2.7 (SE 0.4) -1.8 (SE 0.4) <p>LSMD -0.8 (-1.9 to 0.2); p=0.1224</p> <p>PANSS Marder negative factor score</p> <ol style="list-style-type: none"> -3.5 (SE 0.5) -2.7 (SE 0.5) <p>LSMD -0.8 (95% CI -2.1 to 0.4); p=0.1957</p> <p>CGI-S scale</p> <ol style="list-style-type: none"> -1.1 (SE 0.1) -0.6 (SE 0.1) 	<p>NA</p> <p>NA</p> <p>NS</p> <p>NS</p>	<p>DC due to AE:</p> <ol style="list-style-type: none"> 1. 8 (6%) 2. 7 (5%) <p>Serious AE:</p> <ol style="list-style-type: none"> 1. 1 (1%) 2. 0 (0%) <p>HTN:</p> <ol style="list-style-type: none"> 1. 8 (6%) 2. 2 (2%) <p>Change in heart rate (day 28):</p> <ol style="list-style-type: none"> 1. 11.2 bpm (SD 14.99) 2. 5.9 bpm (SD 13.70) <p>Treatment-emergent AE (mostly GI):</p> <ol style="list-style-type: none"> 1. 88 (70%) 2. 64 (50%) 	<p>NA</p>	<p>Risk of Bias (low/high/unclear):</p> <p>Selection Bias: Low. Computer generated randomization with allocation concealment for patients and investigators. Baseline characteristics were generally balanced between groups.</p> <p>Performance Bias: High. See EMERGENT-2</p> <p>Detection Bias: High. See EMERGENT-2.</p> <p>Attrition Bias: High. High and differential attrition between groups. See EMERGENT-2.</p> <p>Reporting Bias: Low. See EMERGENT-2.</p> <p>Other Bias: Low. Study sponsor was involved in study design and manuscript preparation. Data collection and analysis performed by a third party.</p> <p>Applicability:</p> <p>Patient: n=431 screened, n=256 randomized. Most identified as Black (61%) or White (38%); other races were under-represented. Extensive exclusion criteria including disease severity parameters and comorbid conditions. Inpatient setting limits applicability.</p> <p>Intervention: See EMERGENT-2</p> <p>Comparator: See EMERGNET-2</p> <p>Outcomes: See EMERGENT-2</p> <p>Setting: 18 inpatient sites in the U.S. and Ukraine from April 2021 and December 2022.</p>

				LSMD -0.5 (95% CI -0.8 to -0.3)* PANSS responders (≥30% improvement)* 1. 40/79 (50.6%) 2. 23/91 (25.3%) Difference 25.4% (95% CI 10.8 to 38.6) *NS based on pre-specified testing plan	NS NS			
3. Brannan, et al. 2021. ¹ EMERGENT-1 NCT03697252 PC, DB, MC, inpatient, phase 2 RCT	1. xanomeline/trospium orally twice daily* 2. placebo Dosing: See EMERGENT-2 5 weeks	<u>Demographics:</u> - Male 1. 80% 2. 74% - Age (years) 1. 43.4 (SD 10.1) 2. 41.6 (SD 10.1) - White: 1. 22% 2. 18% - Black or African American 1. 74% 2. 76% - Mean PANSS total: 97 positive: 26 negative: 23 Marder negative factor: 22 - CGI-S: mean 5 <u>Key Inclusion Criteria:</u> - Age 18-60 years - For other criteria, see NCT04659161/EMERGENT-2 <u>Key Exclusion Criteria:</u> - Treatment resistance to antipsychotic medications (>2 adequate courses). First episode or newly diagnosed schizophrenia was not specifically excluded. - For other criteria, see NCT04659161/EMERGENT-2.	<u>ITT:</u> 1. 90 2. 92 <u>mITT:</u> (had post-baseline PANSS) 1. 83 2. 87 <u>PP (completed 5 weeks of treatment):</u> 1. 72 2. 73 <u>Attrition:</u> 1. 18 (20%) 2. 19 (21%)	<u>Primary Endpoint:</u> Change in PANSS after 5 weeks 1. -17.4 (SE 1.8) 2. -5.9 (SE 1.7) LSMD -11.6 (95% CI -16.1 to -7.1); p<0.001 <u>Secondary Endpoints (change after 5 weeks)</u> PANSS positive subscale 1. -5.6 (SE 0.6) 2. -2.4 (SE 0.6) LSMD -3.2 (95% CI -4.8 to -1.7); p<0.001 CGI-S at 5 weeks 1. -1.0 (SE 0.1) 2. -0.3 (SE 0.1) LSMD -0.7 (95% CI -1.0 to -0.4), p<0.001 PANSS negative subscale 1. -3.2 (SE 0.5) 2. -0.9 (SE 0.5) LSMD -2.3 (-3.5 to -1.1); p<0.001 PANSS Marder negative factor score 1. -3.9 (SE 0.5) 2. -1.3 (SE 0.5)	NA NA NA NA	<u>DC due to AE:</u> 1. 2 (2%) 2. 2 (2%) <u>Serious AE:</u> 1. 1 (1%) 2. 0 (0%) <u>Change in heart rate (day 28):</u> 1. 5.9 bpm (SD 13.9) 2. 1.5 bpm (SD 9.6) <u>Any AE (most commonly GI)</u> 1. 54% 2. 43%	NA	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> Low. Computer generated randomization with allocation concealment for patients and investigators. Baseline characteristics were generally balanced between groups. <u>Performance Bias:</u> Unclear. Double blinded but method of blinding was not specified. <u>Detection Bias:</u> Unclear. Method of blinding was not specified. <u>Attrition Bias:</u> Low. High attrition, similar between groups. MMRM used for primary analysis. Sensitivity analyses using different imputation methods had similar direction of effect. <u>Reporting Bias:</u> Low. Pre-specified endpoints reported. Hierarchical testing procedure to control for multiplicity/type 1 error. <u>Other Bias:</u> Unclear. Study sponsor was involved in study design, data analysis, and manuscript preparation. Applicability: <u>Patient:</u> n=250 screened, n=182 randomized. The specific exclusion criteria that were most common was not reported. Most patients identified as Black or White. Extensive exclusion criteria including disease severity parameters and comorbid conditions. Inpatient setting limits applicability. <u>Intervention:</u> See EMERGENT-2. <u>Comparator:</u> See EMERGENT-2 <u>Outcomes:</u> See EMERGENT-2 <u>Setting:</u> 12 inpatient sites in the U.S. between September 2018 and August 2019

				LSMD -2.5 (95% CI - 3.9 to -1.2); p<0.001				
				CGI-S responders at 5 weeks (score of 1 or 2 indicating normal or borderline ill)	NA			
				1. 6%				
				2. 1%				
				Difference 4% (95% CI -3 to 12); p=0.15	NS			

Abbreviations: AE = adverse events; ARR = absolute risk reduction; bpm = beats per minute; CI = confidence interval; CGI-S = Clinical Global Impression-Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; CV = cardiovascular; DC = discontinuation; DB = double blind; ECG = electrocardiogram; GI = gastrointestinal; HIV = human immunodeficiency virus; HTN = hypertension; IBS = irritable bowel syndrome; ITT = intention to treat; LSMD = least square mean difference; MAOI = monoamine oxidase inhibitor; MC = multicenter; MCID = minimum clinically important difference; mITT = modified intention to treat; MMRM = mixed model repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PANSS = positive and negative Syndrome Scale; PBO = placebo; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SSRI = selective serotonin reuptake inhibitor; SUD = substance use disorder; TCA = tricyclic antidepressant; U.S. = United States

Table 3. Pharmacology and Pharmacokinetic Properties.^{12,8}

Parameter	
Mechanism of Action	Xanomeline is a muscarinic receptor agonist which binds to M1 and M4 muscarinic/cholinergic receptors in the CNS. Trospium is a muscarinic receptor antagonist in peripheral tissue and has limited ability to cross into the CNS. The combination allows for cholinergic effects in the CNS with reduced adverse effects in peripheral tissues.
Oral Bioavailability	Bioavailability of xanomeline ~1%; trospium ~15% ⁸ T _{max} = 2 hours (xanomeline); 1 hour (trospium) High-fat meal may increase AUC of xanomeline by 30% and decrease AUC of trospium by 85-90% Xanomeline AUC and C _{max} increased by 50% when dosage increased from 100/20 mg to 125/30 mg twice daily. Trospium increased dose-proportionally for 100/20 mg to 125/30 mg twice daily
Distribution and Protein Binding	Xanomeline: V _d = 10,800 L; Protein binding = 95% Trospium: V _d = 531 L; Protein binding = 80%
Elimination	Xanomeline: metabolites excreted via urine (78%) and feces (12%). Less than 0.01% unchanged in the urine. Trospium: excreted unchanged in the urine (85-90%)
Half-Life	Xanomeline = 5 hours Trospium = 6 hours
Metabolism	Xanomeline: Metabolized via CYP450 enzymes (2D6, 2B6, 1A2, 2C9, and 2C19) and flavin monooxygenases (FMO1 and FMO3) Trospium: ester hydrolysis and glucuronic acid conjugation

Abbreviations: AUC = area under the curve; C_{max} = maximum plasma concentration; CNS = central nervous system; L = liters; T_{max} = time to maximum plasma concentration; V_d = volume of distribution.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COBENFY safely and effectively. See full prescribing information for COBENFY.

COBENFY™ (xanomeline and trospium chloride) capsules, for oral use
Initial U.S. Approval: 2024

INDICATIONS AND USAGE

COBENFY is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist, indicated for the treatment of schizophrenia in adults. (1)

DOSAGE AND ADMINISTRATION

- Assess liver enzymes and bilirubin prior to initiating treatment with COBENFY and as clinically indicated during treatment. (2.1)
- Assess heart rate at baseline and as clinically indicated during treatment with COBENFY. (2.1)
- Recommended starting dosage of COBENFY is 50 mg/20 mg orally twice daily for at least two days, then increase the dosage to 100 mg/20 mg twice daily for at least five days. (2.2)
- Dosage may be increased to 125 mg/30 mg orally twice daily based on patient tolerability and response. (2.2)
- See the full prescribing information for the recommended titration and maximum recommended dosage. (2.2)
- Take at least 1 hour before a meal or at least 2 hours after a meal. Do not open capsules. (2.2)
- Geriatric patients: Recommended starting dosage of COBENFY is 50 mg/20 mg orally twice daily. Consider a slower titration. The maximum recommended dosage is 100 mg/20 mg twice daily. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules (xanomeline/trospium chloride): 50 mg/20 mg, 100 mg/20 mg, 125 mg/30 mg (3)

CONTRAINDICATIONS

COBENFY is contraindicated in:

- urinary retention (4)
- moderate or severe hepatic impairment (4)
- gastric retention (4)
- history of hypersensitivity to COBENFY or trospium chloride (4)
- untreated narrow-angle glaucoma (4)

WARNINGS AND PRECAUTIONS

- Risk of Urinary Retention:** COBENFY can cause urinary retention. Geriatric patients and patients with bladder outlet obstruction and incomplete bladder emptying are at increased risk. Monitor patients for symptoms of acute urinary retention. (5.1)
- Risk of Use in Patients with Hepatic Impairment:** COBENFY is contraindicated in patients with moderate to severe hepatic impairment and is not recommended in patients with mild hepatic impairment. (5.2)

- Risk of Use in Patients with Biliary Disease:** Assess liver enzymes and bilirubin prior to initiating COBENFY and as clinically indicated. Discontinue COBENFY in the presence of signs or symptoms of substantial liver injury. (5.3)
- Decreased Gastrointestinal Motility:** COBENFY may decrease gastrointestinal motility. Use with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention. (5.4)
- Risk of Angioedema:** Angioedema of the face, lips, tongue and/or larynx has been reported with COBENFY. (5.5)
- Risk of Use in Patients with Narrow-angle Glaucoma:** Use COBENFY only if the potential benefits outweigh the risks and with careful monitoring. (5.6)
- Increases in Heart Rate:** COBENFY may increase heart rate. Assess heart rate at baseline and as clinically indicated during treatment with COBENFY. (5.7)
- Anticholinergic Adverse Reactions in Patients with Renal Impairment:** COBENFY is not recommended for use in patients with moderate and severe renal impairment. Anticholinergic adverse reactions are expected to be greater in these patients. (5.8)
- Central Nervous System Effects:** COBENFY may be associated with CNS effects. Advise patients not drive or operate heavy machinery until they know how COBENFY affects them. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (incidence \geq 5% and at least twice placebo) were nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastrointestinal reflux disease. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol Myers-Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs Eliminated by Active Tubular Secretion:** Monitor for increased frequency and/or severity of adverse reactions related to COBENFY and to drugs eliminated by active tubular secretion. (7.1)
- Strong CYP2D6 Inhibitors:** Monitor for increased frequency and/or severity of COBENFY-related adverse reactions. (7.1)
- Sensitive Substrates of CYP3A4 or P-glycoprotein:** Monitor for increased frequency and/or severity of adverse reactions from these substrates. (7.1)
- Antimuscarinic Drugs:** Monitor for increased frequency or severity of anticholinergic adverse reactions. (7.2)

USE IN SPECIFIC POPULATIONS

- Moderate or Severe Renal Impairment:** Not recommended. (8.6)
- Mild Hepatic Impairment:** Not recommended. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2024

Xanomeline-trospium (COBENFY) Safety Edit

Goal(s):

- Promote safe use of xanomeline-trospium in combination with other mental health drugs for schizophrenia.

Length of Authorization:

Up to 12 months

Requires PA:

- Xanomeline-trospium
- Auto-approval requests for people with a claim for xanomeline-trospium in the last 6 months

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is xanomeline-trospium prescribed for an FDA-approved indication?	Yes: Go to #3	No: Pass to RPh. Deny; medical appropriateness
3. Is the intent to prescribe xanomeline-trospium in conjunction with another antipsychotic medication?	Yes: Go to #4	No: Go to #5
4. Is there documentation or provider attestation that the benefits of therapy (e.g. symptom improvement, social function, number of hospitalizations, etc) outweigh potential risks of combination treatment (e.g. hepatic impairment, biliary disease, gastrointestinal and anticholinergic effects, etc)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria

5. Is there documentation or provider attestation that the patient does not have any of the following conditions?

- Concurrent antidepressant that inhibits CYP2D6 (e.g., bupropion, fluoxetine, paroxetine, or duloxetine)
- Urinary retention (e.g., benign prostatic hyperplasia, diabetic cystopathy)
- Untreated narrow-angle glaucoma
- Impaired gastric motility (e.g., gastrointestinal obstructive disorders)
- Mild, moderate or severe hepatic impairment, biliary disease, or elevated liver function tests
- Moderate or severe renal impairment or estimated glomerular filtration rate (eGFR) <60 mL/min

Yes: Approve for 12 months

No: Pass to RPh. Deny; medical appropriateness

*P&T/DUR Review: 2/2025 (SS)
Implementation: 3/10/25*