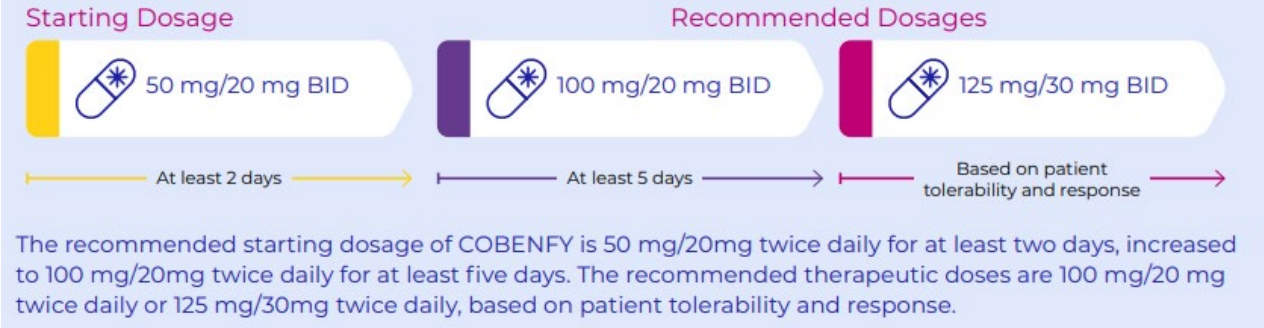
Xanomeline and Trospium Chloride (Cobenfy®)
FDA approved September 2024
(Karuna Therapeutics, Inc. was acquired by Bristol Myers Squibb**)**

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

Mechanism of Action
The antipsychotic effect of xanomeline is not fully understood but is believed to involve its agonist activity at M1 and M4 muscarinic acetylcholine receptors in the CNS. Trospium chloride, a muscarinic antagonist, does not cross the BBB and its primary role is to help mitigate the peripheral side effects associated with muscarinic agonism.

Dosage and Administration

Pre-treatment evaluation	Assess liver enzymes, bilirubin & HR prior to initiating treatment and as clinically indicated during treatment
Administration	Administer at least 1 hour before or 2 hours after a meal. Do not open capsules



Dose Adjustments	
Hepatic impairment	• Mild (Child-Pugh Class A): Not recommended • Moderate to severe (Child-Pugh B or C): Contraindicated
Renal Impairment	• Mild (eGFR 60 to <90 mL/min): No dosage adjustment needed • Moderate to severe (eGFR <60 mL/min): Not recommended
Geriatric	• Initial: Xanomeline 50 mg/trospium 20 mg BID, consider slower titration • Max: Xanomeline 100 mg/trospium 20 mg BID
Anticholinergic CNS Effects	• Consider dose reduction or discontinuation
Liver Injury (jaundice, pruritus, ALT >5x ULN or baseline)	• Discontinue with significant signs of liver injury
Urinary Retention	• Reduce dose, discontinue, or refer for urologic evaluation as indicated

How Supplied	Capsule: (Xanomeline - Trospium) 50 mg-20 mg, 100 mg-20 mg, 125 mg-30 mg. Starter Pack will also be available
Contraindications	• Hypersensitivity to xanomeline, trospium, or any ingredient in Cobenfy • Urinary retention • Moderate or severe liver impairment • Gastric retention • Untreated narrow-angle glaucoma
Precautions	• Cardiovascular: May increase heart rate; assess baseline & monitor as needed. • Gastrointestinal: May reduce motility; use cautiously in GI obstruction, ulcerative colitis, intestinal atony, & myasthenia gravis • Hepatic: Not recommended for mild to severe impairment or active biliary disease; monitor & discontinue if necessary • Immunologic: Angioedema including life threatening cases reported; discontinue immediately & seek medical attention • Neurologic: Anticholinergic CNS effects (dizziness, confusion, hallucination, somnolence); monitor, dose adjustment or discontinuation may be necessary • Ophthalmic: Use in controlled narrow-angle glaucoma only with careful monitoring if benefits

	outweigh risks. • Renal: Moderate to severe impairment may increase anticholinergic events; monitor & consider dose adjustment or discontinuation. Urinary retention with increased risk in geriatrics or pts with bladder outlet obstruction & incomplete emptying; monitor, reduce dose, or discontinue if needed

Adverse Reactions

≥10% Incidence	Cardiovascular	Hypertension (11%)
	Gastrointestinal	Constipation (17%), dyspepsia (18%), nausea (19%), vomiting (15%)
≥3% to 10% Incidence	Cardiovascular	Tachycardia (5%)
	Hepatic	Increased liver enzymes (3%)
	Gastrointestinal	Abdominal pain (8%), diarrhea (6%), GERD (5%), xerostomia (4%)
	Nervous System	Dizziness (5%), drowsiness (3%)
	Ophthalmic	Blurred vision (3%)
≥5% & at least twice the rate of placebo	Nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, & GERD	

Pharmacokinetics	Xanomelime	Trospium
Dose proportionality	• Greater than proportional	• Proportional
Time to steady state	• 3 to 5 days	• 3 to 5 days
Effect of food - High fat meal	• Cmax: Unchanged • AUC: Increased 30%	• Cmax: Reduced 70 to 75% • AUC: Reduced 85 to 90%
Effect of food - Low fat meal	• Cmax: Unchanged • AUC: Unchanged	• Cmax: Reduced 70 to 75% • AUC: Reduced 85 to 90%
T_{max}	• 2 hours	• 1 hour
Half-life	• 5 hours	• 6 hours
Metabolism	• CYP450 & Flavin Monooxygenases	• Ester hydrolysis & glucuronic acid conjugation (not fully characterized)
Excretion	• Urine: 78% (unknown tubular secretion, unchanged: <0.01%) • Feces: 12%	• Urine: unknown (85-90% unchanged, with tubular secretion present) • Feces: unknown

DDI

Drugs eliminated via active tubular secretion	**Monitor for increased side effects (Cobenfy related & active tubular secreted drugs)**
Strong CYP2D6 Inhibitors	Monitor for increased adverse effects
CYP3A4 or P-glycoprotein sensitive substrates	Monitor for increased adverse effects
Antimuscarinic drugs	Monitor for increased anticholinergic adverse effects

Patient Education

- Report symptoms of urinary retention, hepatic impairment/injury or biliary disease.
- Report symptoms of gastrointestinal disorders like ulcerative colitis, intestinal atony, & myasthenia gravis.
- Avoid activities requiring mental alertness until drug effects are known, as it may cause dizziness, confusion, hallucinations, or somnolence.
- Possible side effects include nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, increased heart rate, dizziness, and reflux.

- Report symptoms of angioedema and seek medical attention immediately.
- Take the medication twice daily at least one hour before or 2 hours after a meal, without opening capsules.

Clinical Studies

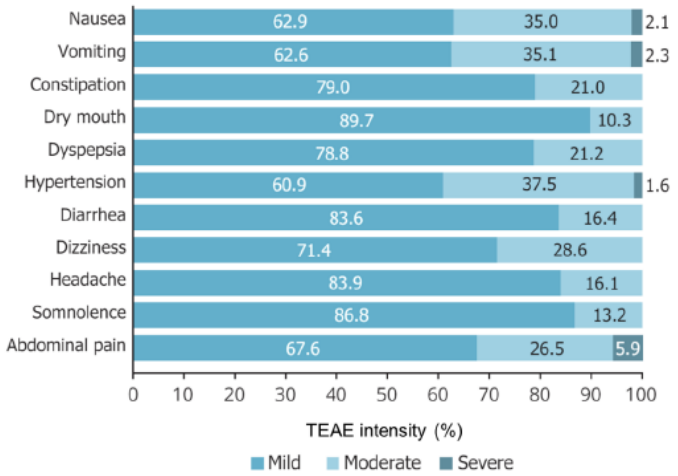
- Efficacy of xenolamine & trospium was assessed in two 5-week, randomized, double blind, placebo-controlled inpatient studies with 470 subjects (aged 19 to 65) diagnosed with schizophrenia (EMERGENT-2 & EMERGENT-3 trials).
  - Demographics: 25% female, 68% Black or African American, 31% White.
  - Primary endpoint was the change from baseline in PANSS total score at week 5 for the Cobenfy group compared to placebo, while the secondary endpoint was the change from baseline in CGI-S score at week 5 (EMERGENT-2).
  - Initial dose of Cobenfy was 50 mg/20 mg BID for the first 2 days, increased to 100 mg/20 mg BID for the remainder of week 1 if tolerated. Titration to 125 mg/30 mg BID occurred on Day 8, with the option to revert to 100 mg/20 mg if not tolerated.
  - No difference in response based on age, sex, or race (no patients over 65).
  - Cobenfy demonstrated statistically significant improvements in schizophrenia symptoms (PANSS & CGI-S scores) over placebo, with consistent results across demographic groups.

			Primary Efficacy Endpoint: PANSS Total Score		
Study Number	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI)[a]
1	COBENFY	117	98.2 (8.9)	-21.2 (1.7)	-9.6 (-13.9, -5.2)*
	Placebo	119	97.7 (9.4)	-11.6 (1.6)	
2	COBENFY	114	96.9 (8.8)	-20.6 (1.6)	-8.4 (-12.4, -4.3)*
	Placebo	120	96.5 (8.8)	-12.2 (1.6)	

The PANSS Total Score may range from 30 to 210; higher scores reflect greater symptom severity.
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in LS mean change from baseline.
* Statistically significantly superior to placebo.

- Long-term safety & efficacy of xanomaline-trospium was assessed in two Phase 3, 52-week, open-label trials with 718 patients, 134 of whom completed one year of treatment. These findings are part of the interim long-term pooled safety outcomes from EMERGENT-4 & EMERGENT-5.

Figure 3-13: Pooled long-term safety analysis from 52-week studies: Intensity of the most common TEAEs (safety population)



- Xanomaline-trospium showed favorable long-term metabolic results, with most patients maintaining or improving metabolic parameters over 52 weeks.
- Most participants (65%) lost weight during the trial, with more showing significant weight decreases (≥7%) than increases (17.6% vs. 4.1%).
- No significant changes in prolactin levels or movement disorder scores were observed over 52 weeks.
- Discontinuation rate was 53% due to reasons such as withdrawn consent (19%), treatment related adverse events (15%), participant lost to follow-up (8%), and non-adherence to protocol (7%).
- Common side effects (≥5%) included nausea, vomiting, constipation, dry mouth, dyspepsia, dizziness, hypertension & diarrhea; mostly mild to moderate and transient.
- Schizophrenia symptom improvements were sustained over 52 weeks, regardless of previous treatment with xanomaline-trospium or placebo (EMERGENT-4 trial). The rate of improvement in negative symptoms persisted throughout the study.

Comments/Role in Therapy

- Cobenfy introduces a novel approach to treating schizophrenia, distinct from traditional dopamine D2 receptor antagonists. Its mechanism combines xanomeline, a dual M1 and M4 muscarinic acetylcholine receptor agonist, with trospium, a peripherally restricted muscarinic receptor antagonist, to reduce peripheral side effects. While further studies and clinical experience will determine whether Cobenfy offers superior efficacy compared to other treatments, it stands out for its muscarinic receptor-targeting mechanism and improved safety profile, particularly in reducing side effects like weight gain, sedation, and movement issues typically linked to D2 antagonists.
- Preliminary data suggest that Cobenfy may help with cognitive symptoms such as blunted affect and lack of motivation. However, these potential benefits need confirmation through focused studies. M4 agonism reduces dopamine release, addressing positive symptoms, while M1 agonism modulates the glutamatergic system, potentially improving cognitive & negative symptoms. Further research is necessary to replicate and expand upon these findings to better understand Cobenfy's impact on cognition.
- Horan et al. found that KarXT *(Cobenfy and KarXT refer to the same drug, renamed after the acquisition)* significantly improved negative symptoms in individuals with schizophrenia, particularly in those with prominent negative symptoms, with effects independent of positive symptom improvements. Additionally, KarXT enhanced both emotional experience and expression. Although the study shows promising results, limitations such as small sample size, short treatment duration, and the complexity of differentiating primary and secondary negative symptoms suggest the need for further research in larger, stable outpatient settings.
- Early studies showed that xanomeline-trospium significantly reduced positive symptoms, with effect size larger than those typically seen with current antipsychotics.
- While Cobenfy shows promise in controlled settings, further evaluation of its real-world effectiveness and patient adherence is necessary. Long-term studies will be critical in assessing its impact, including potential neurological effects. If ongoing research confirms its benefits, Cobenfy could become a valuable option in schizophrenia treatment, particularly for patients resistant or intolerant to existing therapies.

<u>Dosing consideration and practical implications</u>

- Cobenfy's twice-daily dosing may result in higher non-adherence rates compared to less frequent options, such as long acting injectables
- Trospium is FDA approved at 20 mg twice daily for overactive bladder. However, in Cobenfy, the dose may increase to 30 mg BID. While trospium's primary role is to counteract peripheral anticholinergic effects of xanomeline, it may be prudent to monitor for trospium's potential side effects such as xerostomia, headache, constipation, & UTI.

- Trospium's absorption significantly decreases with food, so it's important for patients to take Cobenfy on an empty stomach. If anticholinergic side effects occur, it's important to check that the patient is following the guideline to maintain consistent trospium level.

Safety

- Cobenfy does not carry atypical antipsychotic class or boxed warnings. Regarding the BB warning for increased mortality in elderly patients with dementia-related psychosis, the Emergent 2 and 3 studies included no patients over 65, so adverse effects in the elderly remain unclear.
- In a phase 2, randomized, double-blind, placebo-controlled study (EMERGENT-1), the majority of procholinergic and anticholinergic adverse events with KarXT were mild, occurred within 2 weeks, and were transient. Median AE duration ranged from 1 day (vomiting) to 13 days (dry mouth)
- Cobenfy should not be prescribed to patients with urinary retention, moderate to severe liver impairment, gastric retention, or untreated narrow-angle glaucoma
- Long-term safety and effectiveness remain uncertain due to short study durations and interim data. Larger long-term studies are needed to assess metabolic effects, absence of tardive dyskinesia, and efficacy in addressing negative and cognitive symptoms.

Comparative Effectiveness

- Wright et al. compared KarXT with aripiprazole, risperidone, and olanzapine, concluding that KarXT and the other antipsychotics were more effective than placebo at reducing total, positive and negative symptoms. However, there were no significant differences in short term efficacy among the active treatments. KarXT was less likely to cause weight gain, but short-term data did not provide sufficient evidence to evaluate the risk of tardive dyskinesia. Long term studies are needed for a more comprehensive assessment.
- ICER's independent appraisal committee also assessed KarXT for non-treatment-resistant schizophrenia in March 2024, and reported that
  - -Majority (10-2) found evidence inadequate to demonstrate a net health benefit over aripiprazole.
  - -Slight majority (7-5) found evidence adequate to demonstrate net health benefit over olanzapine and/or risperidone.
- There are no published head-to-head studies comparing KarXT to other investigational drugs or antipsychotics, making it too early to speculate on its superiority compared to less expensive, dopamine-based agents with a long history of use.
- Cobenfy has an anticipated annual cost of $22,200, raising questions about its cost-effectiveness relative to alternatives, though strong demand is expected.

Potential Candidates

- Cobenfy could be considered for patients not responding well to their current medication or experiencing side effects such as involuntary movements, excessive weight gain or uncontrollable diabetes. Its non-dopaminergic mechanism of action offers an alternative to traditional antipsychotics.
- Cobenfy is expected to serve as an adjunctive treatment for patients with inadequate response or low tolerance to traditional D2 receptor-blocking antipsychotics, though more data is needed to support this approach.

Broader application

- Competing drug manufacturers are targeting muscarinic receptors to improve on Cobenfy, focusing on more convenient dosing schedule and greater receptor selectivity. Some focus solely on M1 receptors for cognitive benefits or M4 receptors for antipsychotic effects, unlike Cobenfy which targets both, attempting to create therapies with fewer side effects and enhanced efficacy.

- Researchers are investigating Cobenfy's potential to treat psychosis and agitation associated with Alzheimer's disease, as well as its broader application in neurodegenerative conditions with overlapping schizophrenia symptoms. Ongoing studies are exploring its use for bipolar disorder and cognitive impairment related to psychosis. Muscarinic agonists like Cobenfy may also address unmet needs in dementia-related psychosis, including Parkinsons. If successful, Cobenfy could become a key player in neuropsychiatric care.
- KarXT offers potential as an adjunctive treatment with dopamine-blocking agents, though more data is needed. The Phase III ARISE trial is evaluating its efficacy in adults with schizophrenia with an inadequate response to their current antipsychotic therapy, compared to placebo.
- AbbVie's emraclidine, an M4 selective positive allosteric modulator, shows antipsychotic effects similar to KarXT with improved tolerability and patient adherence due to once-daily dosing and fewer GI side effects, though it may offer fewer cognitive benefits. With several other therapies in development, including Ulotaront (targeting TAAR1), Iclepertin (enhancing cognition via GlyT1 inhibition, granted breakthrough therapy designation by FDA), and valbenazine (studied for schizophrenia in patients unresponsive to antipsychotics), the treatment landscape for schizophrenia is expected to evolve.

Comparative Value

FDA-Approved Third Generation Antipsychotics and Cobenfy for Schizophrenia in Adults and Comparative Cost [36]

Drug and Manufacturer	Dosage Form(s) & Strength(s)	Dosing Regimen	Cost per 30 Days[a]
M1- and M4- Muscarinic Receptor Agonist/Peripheral Muscarinic Receptor Antagonist			
Cobenfy (xanomeline and trospium chloride) *[Bristol-Myers Squibb]*	• Capsules: 50 mg/20 mg, 100 mg/20 mg, 125 mg/30 mg	• 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. Dosage may be increased to 125 mg/30 mg orally twice daily based on patient tolerability and response. • Dosage adjustment: ○ Geriatric patients: Starting dosage of 50 mg/20 mg orally twice daily. The maximum recommended dosage is 100 mg/20 mg twice daily.	$2,220.00
Benzisoxazoles/Benzisothiazoles			
Caplyta (lumateperone) *[Intra-Cellular Therapies, Inc.]*	• Capsules: 42 mg, 21 mg, 10.5 mg	• 42 mg orally once daily. • Dosage adjustment: ○ Moderate or severe hepatic impairment dosage is 21 mg orally once daily.	$1,994.10
Phenylpiperazines/Quinolinones/Benzoxazinones			
Abilify (aripiprazole) *[Various]*	• Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg	• Starting dosage is 10 to 15 mg orally once per day. Recommended target dosage is 10 to 15 mg orally once per day. Maximum dosage is 30 mg orally once per day. • Dosage adjustment: ○ Half of the usual dose in known CYP2D6 poor metabolizers.	Brand: $700.56 - $990.66 Generic: $21.00 - $30.00
Rexulti (brexpiprazole) *[Otsuka Pharmaceutical Co.]*	• Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg	• Starting dosage is 1 mg orally per day. Recommended target dosage is 2 to 4 mg orally per day. Maximum dosage is 4 mg orally per day. • Dosage adjustment: ○ Moderate to severe hepatic impairment or creatinine clearance (CrCl) < 60 mL/minute dosage is 3 mg orally once daily.	$1,765.85
Vraylar (cariprazine) *[AbbVie Inc.]*	• Capsules: 1.5 mg, 3 mg, 4.5 mg, and 6 mg	• Starting dose is 1.5 mg orally daily. Maximum recommended daily dosage is 6 mg orally.	$1,735.86

[a] Estimated cost based on AWP for brands and WAC for generics per Medispan as of 10/09/2024 for 30 days based on the maintenance dosing in the prescribing information.

Formulary Considerations

- Novel mechanism of action with relatively improved safety profile
- Limited market experience and the availability of multiple established alternatives
- Uncertainty that remains about the long-term effectiveness of Cobenfy, and its high cost in relation to available generic treatment options
- Protected class mandatory placement on CareAdvantage formulary
- Recommend formulary placement for BHRS and CA formularies with Prior Authorization

Prior Authorization Criteria:

Diagnosis- FDA approved Indications
Required Documentation—Two previous trials of 2nd or 3rd generation formulary generic antipsychotics
Prescriber Edit: Psychiatrist or in consultation with Psychiatry
Quantity Limit: 2 capsules per day.
Age Limit: 18 years of age and older.

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