COBENFY®
(xanomeline and trospium chloride) capsules
50mg/20mg, 100mg/20mg, 125mg/30mg

First-in-Class Muscarinic Agonist for the Treatment of Schizophrenia in Adults

FOR U.S. AUDIENCES ONLY

What is COBENFY™ (xanomeline and trospium chloride)?

COBENFY is a twice-daily oral medicine for the treatment of schizophrenia in adults.[1]

How does COBENFY work?

COBENFY combines xanomeline, a dual M_1- and M_4-preferring muscarinic receptor agonist, with trospium chloride, a muscarinic receptor antagonist that does not appreciably cross the blood-brain barrier, primarily acting in peripheral tissues.[1]

While the exact mechanism of action of COBENFY is unknown, its efficacy is thought to be due to the agonist activity of xanomeline at M_1 and M_4 muscarinic acetylcholine receptors in the central nervous system.[1]

What is schizophrenia?

Schizophrenia is a persistent and often disabling mental illness that affects how a person thinks, feels and behaves.[2] When not properly managed, symptoms can have a significant impact on daily functioning and overall quality of life.[3,4]

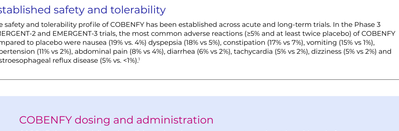
Why is a new approach needed?

People living with schizophrenia often experience a cycle of discontinuing and switching therapies.[5] Studies have shown that approximately 40% of people with schizophrenia do not respond to therapy, and up to 60% experience a partial or inadequate improvement or intolerable side effects during therapy.[6,7]

Historically, antipsychotic medicines approved to treat schizophrenia have relied on the same primary pathways in the brain.[8,9] By leveraging a novel pathway, COBENFY offers a new option to help manage this challenging condition.

Introducing a new class

The journey to a new class of treatment for schizophrenia has been decades in the making.[10-17] COBENFY introduces a fundamentally new pharmacological approach to treating schizophrenia—one that has the potential to transform the treatment paradigm.



Not effective of all approvals and formulations

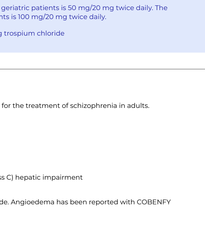
Clinical trial results

The FDA approval of COBENFY is supported by data from the EMERGENT clinical program, which includes three placebo-controlled efficacy and safety trials and two open-label trials evaluating the long-term safety and tolerability of COBENFY for up to one year.

The Phase 3 EMERGENT-2 and EMERGENT-3 trials were five-week, inpatient trials that evaluated the efficacy, safety and tolerability of COBENFY compared to placebo in adults with schizophrenia. In both trials, COBENFY met its primary endpoint, demonstrating statistically significant reductions of schizophrenia symptoms compared to placebo, as measured by the Positive and Negative Syndrome Scale (PANSS) at week five.[1]

Further, in EMERGENT-2, COBENFY demonstrated a statistically significant 0.6 change (-1.2 COBENFY vs. -0.7 placebo; p<0.0001) in the Clinical Global Impression-Severity (CGI-S) score, a secondary endpoint in the trial.[18] The CGI-S is a validated clinician-rated scale that measures an individual's current illness state and overall clinical state on a 1- to 7-point scale.[19]

A robust reduction of schizophrenia symptoms



What is PANSS?

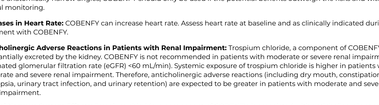
The Positive and Negative Syndrome Scale (PANSS) is a validated rating instrument with strong reliability and sensitivity used to measure symptom severity and assess treatment efficacy.[20,21] The PANSS total score may range from 30 to 210, with higher scores reflecting greater overall symptom severity.[20]

Established safety and tolerability

The safety and tolerability profile of COBENFY has been established across acute and long-term trials. In the Phase 3 EMERGENT-2 and EMERGENT-3 trials, the most common adverse reactions (≥5% and at least twice placebo) of COBENFY compared to placebo were nausea (19% vs. 4%) dyspepsia (18% vs 5%), constipation (17% vs 7%), vomiting (15% vs 1%), hypertension (11% vs 2%), abdominal pain (8% vs 4%), diarrhea (6% vs 2%), tachycardia (5% vs 2%), dizziness (5% vs 2%) and gastroesophageal reflux disease (5% vs. <1%).[1]

COBENFY dosing and administration

COBENFY is a twice-daily oral medicine to be taken on an empty stomach—at least 1 hour before or at least 2 hours after a meal. COBENFY offers flexible titration and two recommended doses*:



The recommended starting dosage of COBENFY is 50 mg/20mg twice daily for at least two days, increased to 100 mg/20mg twice daily for at least five days. The recommended therapeutic doses are 100 mg/20 mg twice daily or 125 mg/30mg twice daily, based on patient tolerability and response.

The recommended starting dosage of COBENFY in geriatric patients is 50 mg/20 mg twice daily. The maximum recommended dosage in geriatric patients is 100 mg/20 mg twice daily.

*COBENFY dose is expressed as mg xanomeline/mg trospium chloride

INDICATION

COBENFY™ (xanomeline and trospium chloride) is indicated for the treatment of schizophrenia in adults.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

COBENFY is contraindicated in patients with:

- urinary retention
- moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment
- gastric retention
- history of hypersensitivity to COBENFY or trospium chloride. Angioedema has been reported with COBENFY and trospium chloride.
- untreated narrow-angle glaucoma

WARNINGS AND PRECAUTIONS

Risk of Urinary Retention: COBENFY can cause urinary retention. Geriatric patients and patients with clinically significant bladder outlet obstruction and incomplete bladder emptying (e.g., patients with benign prostatic hyperplasia (BPH), diabetic cystopathy) may be at increased risk of urinary retention.

COBENFY is contraindicated in patients with pre-existing urinary retention and is not recommended in patients with moderate or severe renal impairment.

In patients taking COBENFY, monitor for symptoms of urinary retention, including urinary hesitancy, weak stream, incomplete bladder emptying, and dysuria. Instruct patients to be aware of the risk and promptly report symptoms of urinary retention to their healthcare provider. Urinary retention is a known risk factor for urinary tract infections. In patients with symptoms of urinary retention, consider reducing the dose of COBENFY, discontinuing COBENFY, or referring patients for urologic evaluation as clinically indicated.

Risk of Use in Patients with Hepatic Impairment: Patients with hepatic impairment have higher systemic exposures of xanomeline, a component of COBENFY, compared to patients with normal hepatic function, which may result in increased incidence of COBENFY-related adverse reactions.

COBENFY is contraindicated in patients with moderate or severe hepatic impairment. COBENFY is not recommended in patients with mild hepatic impairment.

Assess liver enzymes prior to initiating COBENFY and as clinically indicated during treatment.

Risk of Use in Patients with Biliary Disease: In clinical studies with COBENFY, transient increases in liver enzymes with rapid decline occurred, consistent with transient biliary obstruction due to biliary contraction and possible gallstone passage.

COBENFY is not recommended for patients with active biliary disease such as symptomatic gallstones. Assess liver enzymes and bilirubin prior to initiating COBENFY and as clinically indicated during treatment. The occurrence of symptoms such as dyspepsia, nausea, vomiting, or upper abdominal pain should prompt assessment for gallbladder disorders, biliary disorders, and pancreatitis, as clinically indicated.

Discontinue COBENFY in the presence of signs or symptoms of substantial liver injury such as jaundice, pruritus, or alanine aminotransferase levels more than five times the upper limit of normal or five times baseline values.

Decreased Gastrointestinal Motility: COBENFY contains trospium chloride. Trospium chloride, like other antimuscarinic agents, may decrease gastrointestinal motility. Administer COBENFY with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention. Use COBENFY with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

Risk of Angioedema: Angioedema of the face, lips, tongue, and/or larynx has been reported with COBENFY and trospium chloride, a component of COBENFY. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, discontinue COBENFY and initiate appropriate therapy and/or measures necessary to ensure a patent airway. COBENFY is contraindicated in patients with a history of hypersensitivity to trospium chloride.

Risk of Use in Patients with Narrow-angle Glaucoma: Pupillary dilation may occur due to the anticholinergic effects of COBENFY. This may trigger an acute angle closure attack in patients with anatomically narrow angles. In patients known to have anatomically narrow angles, COBENFY should only be used if the potential benefits outweigh the risks and with careful monitoring.

Increased In Heart Rate: COBENFY can increase heart rate. Assess heart rate at baseline and as clinically indicated during treatment with COBENFY.

Anticholinergic Adverse Reactions in Patients with Renal Impairment: Trospium chloride, a component of COBENFY, is substantially excreted by the kidney. COBENFY is not recommended in patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <60 mL/min). Systemic exposure of trospium chloride is higher in patients with moderate and severe renal impairment. Therefore, anticholinergic adverse reactions (including dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in patients with moderate and severe renal impairment.

Central Nervous System Effects: Trospium chloride, a component of COBENFY, is associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported with trospium chloride, including dizziness, confusion, hallucinations, and somnolence. Monitor patients for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how COBENFY affects them. If a patient experiences anticholinergic CNS effects, consider dose reduction or drug discontinuation.

Most Common Adverse Reactions (≥5% and at least twice placebo): nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease.

Use in Specific Populations:

- Moderate or Severe Renal Impairment: Not recommended
- Mild Hepatic Impairment: Not recommended

COBENFY (xanomeline and trospium chloride) is available in 50mg/20mg, 100mg/20mg, and 125mg/30mg capsules.

Please see U.S. Full Prescribing Information, including Patient Information.

For more information, visit COBENFY.com.

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