PDL DRUG REVIEW

Proprietary Name: Cobenfy®
Common Name: xanomeline and trospium chloride
PDL Category: Psychotherapeutic Combination

Comparable Products	Preferred Drug List Status
Atypical Antipsychotics	Preferred

Pharmacology/Usage: Cobenfy® is a combination of xanomeline (a muscarinic agonist) and trospium chloride (a muscarinic antagonist). The mechanism of action of xanomeline for its approved indication is not clear; however, its efficacy is thought to be due to its agonist activity at M1 and M4 muscarinic acetylcholine receptors in the CNS. Trospium chloride antagonizes the muscarinic receptors primarily in the peripheral tissues.

Indication: For the treatment of schizophrenia in adults.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. However, there are risks to the mother associated with untreated schizophrenia. There is a pregnancy exposure registry that monitors outcomes in women exposed to psychiatric medications, including Cobenfy®, during pregnancy. Healthcare providers are encouraged to advise patients to register by calling 1-866-961-2388 or visiting online. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Capsules (available as xanomeline/trospium chloride): 50mg/20mg, 100mg/20mg, and 125mg/30mg.

Recommended Dosage: Recommended testing and monitoring prior to initiation and during treatment:

- Assess liver enzymes and bilirubin prior to starting treatment and as clinically indicated during treatment.
- Assess heart rate at baseline and as clinically indicated during treatment.

The recommended dosage:

- Starting dosage is 50mg/20mg PO BID for at least 2 days.
- Increase the dosage to 100mg/20mg PO BID for at least 5 days.
- May increase to 125mg/30mg PO BID based on patient tolerability and response.
- Maximum recommended dosage is 125mg/30mg PO BID.

Administer at least one hour before a meal or at least two hours after a meal. Do not open the capsules.

The recommended starting dosage in geriatric patients is 50mg/20mg PO BID. Consider a slower titration for geriatric patients, with the maximum recommended dosage in geriatric patients being 100mg/20mg PO BID.

The recommended dosage in patients with mild renal impairment is the same as the recommended dosage for patients with normal renal function; however, use of Cobenfy® is not recommended in patients with moderate or

severe renal impairment (eGFR <60ml/min). Use of Cobenfy® is not recommended in patients with mild hepatic impairment, and use of Cobenfy® is contraindicated in patients with moderate or severe hepatic impairment.

Drug Interactions: CYP2D6 contributes significantly to the metabolism of xanomeline. Concomitant use of Cobenfy® with strong CYP2D6 inhibitors may increase plasma concentrations of xanomeline. Monitor patients for increased frequency and/or severity of adverse reactions related to Cobenfy® in patients taking Cobenfy® with strong inhibitors of CYP2D6.

Concomitant use of Cobenfy® with drugs that are eliminated by active tubular secretion may increase plasma concentrations of trospium, and/or the concomitantly used drug due to competition for this elimination pathway, which may increase the frequency and/or severity of adverse reactions from Cobenfy® or the drug eliminated by active tubular secretion. Monitor patients for increased frequency and/or severity of adverse reactions related to Cobenfy® and adverse reactions related to drugs eliminated by active tubular secretion in patients concomitantly receiving such drugs.

Xanomeline transiently inhibits CYP3A4 locally in the gut but not systemically. Concomitant use of Cobenfy® with oral drugs that are sensitive substrates of CYP3A4 may result in increased plasma concentrations of the oral drugs that are sensitive substrates of CYP3A4. Monitor patients for increased frequency and/or severity of adverse reactions related to oral drugs that are sensitive substrates of CYP3A4 in patients taking Cobenfy® with such substrates.

Xanomeline transiently inhibits P-gp locally in the gut but not systemically. Concomitant use of Cobenfy® with oral drugs that are substrates of P-gp may result in increased plasma concentrations of the oral drugs that are substrates of P-gp. Monitor patients for increased frequency and/or severity of adverse reactions related to oral drugs that are narrow therapeutic index substrates of P-gp in patients taking Cobenfy® with such substrates.

Concomitant use of Cobenfy® with other antimuscarinic drugs that produce anticholinergic adverse reactions (e.g., dry mouth, constipation) may increase the frequency and/or severity of such effects. Monitor patients for increased frequency and/or severity of anticholinergic adverse reactions when Cobenfy® is used concomitantly with other antimuscarinic drugs.

Cobenfy® may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Dosage adjustment of concomitant medications may be necessary based on clinical response and tolerability.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Cobenfy®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included nausea (15%), dyspepsia (13%), constipation (10%), vomiting (14%), hypertension (9%), abdominal pain (4%), diarrhea (4%), tachycardia (3%), dizziness (3%), gastroesophageal reflux disease (>4%), dry mouth (2%), somnolence (1%), vision blurred (3%), salivary hypersecretion (2%), orthostatic hypotension (1%), cough (1%), and extrapyramidal symptoms (EPS, non-akathisia; >1%).

Cobenfy® can cause urinary retention. Geriatric patients and patients with clinically significant bladder outlet obstruction and incomplete bladder emptying may be at increased risk of urinary retention. Cobenfy® is contraindicated in patients with preexisting urinary retention. Monitor for symptoms of urinary retention, which 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.

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

starting Cobenfy® and as clinically indicated during treatment. Discontinue Cobenfy® in the presence of signs or symptoms of substantial liver injury.

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.

Angioedema of the face, lips, tongue, and/or larynx has been reported with Cobenfy® and trospium chloride. If involvement of the tongue, hypopharynx, or larynx occurs, discontinue Cobenfy® and start appropriate therapy and/or measures necessary to ensure a patent airway.

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.

Cobenfy® can increase heart rate. Assess heart rate at baseline and as clinically indicated during Cobenfy® treatment.

Trospium chloride is associated with anticholinergic CNS effects. Monitor patients for signs of anticholinergic CNS effects, especially 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.

Contraindications: In patients with:

- Urinary retention.
- Moderate or severe hepatic impairment.
- Gastric retention.
- History of hypersensitivity to Cobenfy® or trospium chloride.
- Untreated narrow-angle glaucoma.

Manufacturer: Bristol-Myers Squibb

Analysis: The efficacy of Cobenfy® for the treatment of schizophrenia in adults was assessed in two placebo-controlled studies with identical designs (N=470). Study 1 and Study 2 were five-week, randomized, double-blind, placebo-controlled, multicenter studies that included adults with a diagnosis of schizophrenia per DSM-5 criteria.

Demographic and baseline disease characteristics were similar for the Cobenfy® and placebo groups. The median age of included patients was 46 years (range 19 to 65), while 25% were female and 68% were Black or African American.

The primary efficacy measure was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at week 5. The PANSS is a 30-item scale that measures symptoms of schizophrenia. Each item is rated by a clinician on a seven-point scale. A score of 1 indicates the absence of symptoms, and a score of 7 indicates extremely severe symptoms. The PANSS total score may range from 30 to 210, with higher scores reflecting greater overall symptom severity.

In Study 1 (EMERGENT-2) and Study 2 (EMERGENT-3), patients randomized to Cobenfy® demonstrated a statistically significant reduction from baseline to week 5 in the PANSS Total Score compared to the placebo group. A secondary endpoint, the change from baseline to week 5 on the Clinical Global Impression-Severity (CGI-S) score, was statistically significant for Cobenfy® compared to placebo in Study 1. The CGI-S is a validated clinician-rated scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale. Results of the primary endpoint are presented in the table below, which was adapted from the prescribing information.

	Primary Efficacy Endpoint: PANSS Total Score				
Study Number	**Treatment Group**	**N**	**Mean Baseline Score**	**LS Mean change from baseline**	**Placebo-subtracted difference**
1	Cobenfy®	117	98.2	-21.2	-9.6 *
	Placebo	119	97.7	-11.6	
2	Cobenfy®	114	96.9	-20.6	-8.4 *
	Placebo	120	96.5	-12.2	

*Statistically significantly superior to placebo.

Place in Therapy: Cobenfy® is a combination of xanomeline (a muscarinic agonist) and trospium chloride (a muscarinic antagonist), indicated for the treatment of schizophrenia in adults. Schizophrenia is one of the most disabling behavioral health illnesses. Characteristics of schizophrenia include both positive and negative symptoms.[2]

Use of Cobenfy® is contraindicated in patients with moderate or severe hepatic impairment, as well as urinary and gastric retention and untreated narrow-angle glaucoma. The efficacy of Cobenfy® was assessed in phase 3, multicenter, double-blind, randomized studies that included patients diagnosed with schizophrenia per DSM-5 criteria. The primary efficacy measure of the two studies discussed above was the change from baseline in PANSS total score at week 5, and results suggested that the Cobenfy® group demonstrated a statistically significant reduction from baseline to week 5 in the PANSS total score compared to the placebo group. The drug demonstrated better tolerability than existing antipsychotics, with fewer side effects like weight gain and extrapyramidal symptoms.[3] Cobenfy® is a first-in-class combination muscarinic agonist/muscarinic antagonist that provides another treatment option for schizophrenia. Head-to-head active comparator studies were not currently found.

Summary

There is no evidence at this time to support that Cobenfy® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Cobenfy® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred Step 3 (atypical antipsychotics step therapy requirements apply)**

References

[1] Cobenfy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2024.
[2] UpToDate online. Schizophrenia in adults: Clinical features, assessment, and diagnosis. Accessed February 2025.
[3] Hasan, A. H., & Abid, M. A. (2024). Cobenfy (Xanomeline-Trospium Chloride): A new frontier in schizophrenia management. *Cureus, 16*(10), e71131. https://doi.org/10.7759/cureus.71131

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