Xanomeline and trospium chloride (Cobenfy™)	
Dosing	Initial: 50 mg/20 mg BID for at least 2 days, then increase to 100 mg/20 mg BID for at least 5 days. Max dose: 125 mg/30 mg BID Altered kidney function: eGFR <60 mL/min use is not recommended Altered liver function: Mild impairment use is not recommended, Moderate-severe impairment use is contraindicated
Indication	Schizophrenia
Mechanism of Action	**Xanomeline** is a M1/M4 preferring muscarinic agonist. Works for psychosis by modulating dopamine via stimulatory M1 receptor activation and inhibitory M4 autoreceptor activation. Leads to decreased presynaptic dopamine release in the striatal regions. **Trospium chloride** is a peripheral muscarinic antagonist. It blocks the activation of peripheral muscarinic receptors therefore reducing the severe cholinergic side effects of xanomeline.
Side Effects	Common: Nausea, vomiting, dyspepsia, constipation, hypertension, dry mouth, abdominal pain, diarrhea, tachycardia Less common: orthostatic hypotension, dizziness, GERD, increased liver enzymes
	NOTE: in the 5-week clinical trials there was no significant weight gain, EPS, akathisia, changes in prolactin, A1c or lipids.
Monitoring	Liver enzymes and bilirubin prior to initiation, then as clinically appropriate Heart rate at baseline, then clinically as indicated
Contraindications	History of hypersensitivity to xanomeline or trospium Urinary retention Moderate-severe liver impairment Gastric retention Untreated narrow-angle glaucoma
Drug Interactions ***not a complete list***	Antimuscarinic drugs (ex. Benztropine, oxybutynin, olanzapine, quetiapine, clozapine): combination may increase frequency or severity of anticholinergic side effects Strong CYP2D6 inhibitors (ex. Fluoxetine, paroxetine, bupropion): may increase serum concentration of xanomeline CYP3A4 substrates (ex. Buspirone): xanomeline may increase serum concentration of 3A4 substrates Substrates of P-glycoprotein with narrow therapeutic index (ex. Apixaban, digoxin, colchicine): xanomeline may increase plasma concentrations of these medications Medications eliminated by active tubular secretion (ex, digoxin, morphine): may increase plasma concentrations of trospium chloride
Counseling Points	Administer >1 hour before or >2 hours after a meal Do not open capsules
Availability	Can be obtained from a retail pharmacy Cash price is ~$1,800 Medicaid: will be added as a non-preferred drug to PDL. Requires trial and failure of **ONE** preferred antipsychotic agent Patient assistance program: https://www.cobenfy.com/support-program
How Supplied	Starter titration pack contains: 1 mixed blister wallet: Four 50/20 mg capsules and ten 100 mg/20 mg capsules AND 3 wallets: Fourteen 100/20 mg capsules in each wallet 50/20 mg capsules 100/20 mg capsules 125/30 mg capsules
Summary of Evidence	Three, 5-week, randomized, placebo-controlled trials enrolled patients aged 18-65 hospitalized with an acute exacerbation of psychosis. Average initial total PANSS scores across the studies were 97-98 indicating markedly ill patients. PANSS scores significantly decreased compared to placebo with a 17.4-20.1 reduction in total scores. Effect size of 0.60-0.81 was found for xanomeline/trospium across the 3 studies.

Limitations	Has not been studied in patients <18 or >65 years old Has only been studied as a monotherapy for schizophrenia Data for use >5 weeks has not been published yet No available data in pregnancy or lactation No head-to-head trials with xanomeline/ trospium chloride compared to available antipsychotics Patients newly diagnosed with schizophrenia or in their first treatment episode were excluded from the clinical trials Patients with treatment resistant schizophrenia were excluded from clinical trials