COBENFY® 50 mg/20 mg

COBENFY® 100 mg/20 mg

COBENFY® 125 mg/30 mg

CAPSULES

Cobenfy 50/20 mg capsule contains 50 mg of xanomeline and 20 mg of trospium chloride
Cobenfy 100 mg/20 mg capsule contains 100 mg of xanomeline and 20 mg of trospium chloride
Cobenfy 125 mg/30 mg capsule contains 125 mg of xanomeline and 30 mg of trospium chloride

1 INDICATIONS AND USAGE

COBENFY is indicated for the treatment of schizophrenia in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Testing and Monitoring Prior to Initiation and During Treatment with COBENFY

- Assess liver enzymes and bilirubin prior to initiating COBENFY and as clinically indicated during treatment *[see Contraindications (4) and Warnings and Precautions (5.2, 5.3)]*.
- Assess heart rate at baseline and as clinically indicated during treatment *[see Warnings and Precautions (5.7)]*.

2.2 Recommended Dosage and Administration

The recommended dosage of COBENFY is as follows:

- The recommended starting dosage is one 50 mg/20 mg capsule (contains 50 mg of xanomeline and 20 mg of trospium chloride) orally twice daily for at least two days.
- Increase the dosage to one 100 mg/20 mg capsule (contains 100 mg of xanomeline and 20 mg of trospium chloride) orally twice daily for at least five days.
- The dosage may be increased to one 125 mg/30 mg capsule (contains 125 mg of xanomeline and 30 mg of trospium chloride) orally twice daily based on patient tolerability and response *[see Clinical Studies (14)]*.
- Maximum recommended dosage is 125 mg/30 mg orally twice daily.

Administer COBENFY orally at least one hour before a meal or at least two hours after a meal *[see Clinical Pharmacology (12.3)]*.
Swallow the capsules whole. Do not open the capsules. There is no data on using the capsules this way.

2.3 Dosage Recommendations in Geriatric Patients

The recommended starting dosage of COBENFY in geriatric patients is one 50 mg/20 mg capsule orally twice daily. Consider a slower titration for geriatric patients. The maximum recommended dosage in geriatric patients is one 100 mg/20 mg capsule twice daily *[see Warnings and Precautions (5.1, 5.8) and Use in Specific Populations (8.5)]*.

3 DOSAGE FORMS AND STRENGTHS

COBENFY is available as:

- 50 mg/20 mg (xanomeline/trospium chloride): Buff capsules imprinted with Karuna 50/20 mg
- 100 mg/20 mg (xanomeline/trospium chloride): Brown capsules imprinted with Karuna 100/20 mg
- 125 mg/30 mg (xanomeline/trospium chloride): Swedish Orange capsules imprinted with Karuna 125/30 mg

4 CONTRAINDICATIONS

COBENFY is contraindicated in patients with:

- urinary retention *[see Warnings and Precautions (5.1)]*.
- moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment *[see Warnings and Precautions (5.2)]*.
- gastric retention *[see Warnings and Precautions (5.4)]*.
- Hypersensitivity to COBENFY or trospium chloride or xanomeline or to any of the excipients listed in section 11 (description). Angioedema has been reported with COBENFY and trospium chloride *[see Warnings and Precautions (5.5)]*.
- untreated narrow-angle glaucoma *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Urinary Retention

COBENFY can cause urinary retention *[see Adverse Reactions (6.1)]*. 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 *[see Use in Specific Populations (8.5)]*.

COBENFY is contraindicated in patients with pre-existing urinary retention *[see Contraindications (4)]* and is not recommended in patients with moderate or severe renal impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

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.

5.2 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 *[see Clinical Pharmacology (12.3)]*.

COBENFY is contraindicated in patients with moderate or severe hepatic impairment *[see Contraindications (4)]*. COBENFY is not recommended in patients with mild hepatic impairment *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

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

5.3 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 *[see Adverse Reactions (6.1)]*.

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.

5.4 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 *[see Contraindications (4)]*. Use COBENFY with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

5.5 Risk of Angioedema

Angioedema of the face, lips, tongue, and/or larynx has been reported with COBENFY and trospium chloride, a component of COBENFY *[see Adverse Reactions (6.2)]*. 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.

5.6. 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 *[see Contraindications (4)]*.

5.7. Increases in Heart Rate

COBENFY can increase heart rate *[see Adverse Reactions (6.1)].* Assess heart rate at baseline and as clinically indicated during treatment with COBENFY *[see Dosage and Administration (2.1)]*.

5.8 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 *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. 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.

5.9 Central Nervous System Effects

Trospium chloride, a component of COBENFY, is associated with anticholinergic central nervous system (CNS) effects *[see Adverse Reactions (6.1)]*. 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. If a patient experiences anticholinergic CNS effects, consider dose reduction or drug discontinuation.

5.10 Effects on ability to drive and use machines

Advise patients not to drive or operate heavy machinery until they know how COBENFY affects them.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risk of Urinary Retention *[see Warnings and Precautions (5.1)]*
- Risk of Use in Patients with Hepatic Impairment *[see Warnings and Precautions (5.2)]*
- Risk of Use in Patients with Biliary Disease *[see Warnings and Precautions (5.3)]*
- Decreased Gastrointestinal Motility *[see Warnings and Precautions (5.4)]*
- Risk of Angioedema *[see Warnings and Precautions (5.5)]*
- Risk of Use in Patients with Narrow-angle Glaucoma *[see Warnings and Precautions (5.6)]*
- Increases in Heart Rate *[see Warnings and Precautions (5.7)]*
- Anticholinergic Adverse Reactions in Patients with Renal Impairment *[see Warnings and Precautions (5.8)]*
- Central Nervous System Effects *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

COBENFY was evaluated for safety in a total of 1,594 subjects exposed to one or more doses, including 1,135 adult patients with schizophrenia and 389 healthy subjects. A total of 347 COBENFY-treated patients had at least 6 months of exposure and 150 patients had at least 1 year of exposure (defined as ≥ 50 weeks) from open-label studies.

The adverse reaction findings are based on two pooled 5-week, placebo-controlled, flexible-dose studies in 504 adult patients with schizophrenia in which COBENFY or placebo was started at an initial dose of 50 mg/20 mg twice daily for the first 2 days followed by 100 mg/20 mg twice daily for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing was titrated to 125 mg/30 mg twice daily unless the patient could not tolerate it. All patients had the option to return to 100 mg/20 mg twice daily for the remainder of the treatment period *[see Clinical Studies (14)]*.

In the 5-week placebo-controlled studies, 6% of patients treated with COBENFY and 4% of placebo-treated patients discontinued participation due to adverse reactions. Adverse reactions that led to study discontinuation in ≥1% of patients treated with COBENFY include nausea (2%) and vomiting (1%).

The most common adverse reactions (≥5% and at least twice placebo) were nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease.

Adverse reactions reported with COBENFY at an incidence of at least 2% in patients exposed to COBENFY and greater than the rate of placebo are shown in Table 1.

Table 1: Adverse Reactions Reported in ≥2% of COBENFY-Treated Patients and Greater than Rate of Placebo in Two 5-week Schizophrenia Trials

	COBENFY (N=251)	Placebo (N=253)
Nausea	19%	4%
Dyspepsia[a]	18%	5%
Constipation	17%	7%
Vomiting	15%	1%
Hypertension[b]	11%	2%
Abdominal Pain[c]	8%	4%
Diarrhea	6%	2%
Tachycardia[d]	5%	2%
Dizziness	5%	2%
Gastroesophageal reflux disease	5%	<1%
Dry mouth	4%	2%
Somnolence	3%	2%
Vision blurred	3%	0%
Salivary hypersecretion	2%	0%
Orthostatic hypotension	2%	1%
Cough[e]	2%	1%
Extrapyramidal symptoms (EPS), non-akathisia[f]	2%	<1%

[a] Dyspepsia includes dyspepsia, esophageal discomfort
[b] Hypertension includes hypertension, blood pressure increased, labile hypertension, orthostatic hypertension
[c] Abdominal Pain includes abdominal discomfort, abdominal pain upper, abdominal pain, abdominal pain lower, abdominal tenderness
[d] Tachycardia includes tachycardia, heart rate increased, sinus tachycardia
[e] Cough: includes cough, productive cough
[f] EPS (non-akathisia) includes dyskinesia, drooling, dystonia, extrapyramidal disorder, muscle contraction involuntary, muscle spasms

Increases in Heart Rate

In a dedicated 8-week clinical study, 24-hour ambulatory blood pressure monitoring (ABPM) was conducted in 133 patients with schizophrenia. A total of 95 patients had acceptable ABPM recordings at both baseline and Week 8. In that group, there was a mean change in 24-hour heart rate of 9.8 beats per minute (bpm) (95% CI 7.5, 12.2) from baseline to Week 8.

In the two placebo-controlled schizophrenia studies, COBENFY was associated with increases in heart rate compared to placebo, with peak elevation occurring on Day 8 of study treatment (13.5 bpm in the COBENFY group and 4.0 bpm in the placebo group), partially attenuating with continued dosing (11.4 bpm in the COBENFY group and 5.5 bpm in the placebo group at Week 5).

Liver Enzyme Elevations

In the 5-week, placebo-controlled schizophrenia studies, the proportions of patients with ALT or AST elevations of ≥3 times the upper limits of the normal reference range were 2.8% (6/214) for COBENFY-treated patients compared to 0.4% (1/224) of placebo-treated patients. Twenty-five (1.6%) of the total 1,594 subjects exposed to COBENFY had elevated liver enzymes. The majority of liver enzyme elevations occurred within the first month of treatment and resolved with continued COBENFY use, suggestive of liver adaptation; some cases required treatment interruption, and one was associated with an increase in bilirubin.

Urinary Retention

In the 5-week, placebo-controlled studies, urinary retention (urinary hesitation, dysuria, and urinary retention) was reported in 0.8% of COBENFY-treated patients and 0.4% on placebo. In the long-term, open-label studies, urinary retention was reported in 3.5% of COBENFY-treated patients. Urinary retention was more common in males, geriatric patients, and those with certain risk factors *[see Warnings and Precautions (5.1)]*. Urinary retention occurred at all doses but was predominately observed at the maximum COBENFY dose. In the long-term, open-label studies, urinary tract infections were reported in 2.3% of COBENFY-treated patients and were more commonly reported in females than males. Of the total 1,594 subjects exposed to COBENFY (including healthy volunteers and patients with schizophrenia or other conditions), four subjects required a Foley catheter, including one with elevated serum creatinine and one with urinary tract infections. Four subjects with urinary retention required reduction of COBENFY dose, four discontinued COBENFY, and four received medications for the treatment of benign prostatic hyperplasia (BPH).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of trospium chloride, one of the components of COBENFY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Cardiovascular* – chest pain, hypertensive crisis, palpitations, supraventricular tachycardia, syncope
- *Gastrointestinal* – gastritis
- *General* – rash
- *Musculoskeletal* – rhabdomyolysis
- *Nervous System* – confusion, delirium, dizziness, hallucinations, somnolence, vision abnormal
- *Skin and subcutaneous tissue disorders* – angioedema, anaphylactic reaction, Stevens-Johnson syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

7 DRUG INTERACTIONS

7.1 Clinically Significant Drug Interactions with COBENFY

Table 2 displays clinically significant drug interactions with COBENFY.

Table 2: Clinically Significant Drug Interactions with COBENFY

Strong Inhibitors of CYP2D6

Clinical Implication:	CYP2D6 contributes significantly to the metabolism of xanomeline, a component of COBENFY. Concomitant use of COBENFY with strong CYP2D6 inhibitors may increase plasma concentrations of xanomeline, which may increase the frequency and/or severity of adverse reactions from COBENFY *[see Clinical Pharmacology (12.3)]*. Examples of strong CYP2D6 inhibitors[a] include buproprion, fluoxetine, paroxetine, quinidine and terbinafine.
Prevention or Management:	Monitor patients for increased frequency and/or severity of adverse reactions related to COBENFY in patients taking COBENFY with strong inhibitors of CYP2D6.
Drugs Eliminated by Active Tubular Secretion	
Clinical Implication:	Concomitant use of COBENFY with drugs that are eliminated by active tubular secretion may increase plasma concentrations of trospium a component of COBENFY, 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 *[see Clinical Pharmacology (12.3)]*. Though trospium chloride was shown not to affect pharmacokinetics of digoxin, an interaction with other active substances eliminated by active tubular secretion cannot be excluded. Examples of drugs eliminated by active tubular secretion include: - OAT1/OAT3 transporter [b]: adefovir, oseltamivir, tenofovir, cefaclor, ceftizoxime, ciprofloxacin, penicillin G, bumetanide, furosemide, baricitinib, famotidine, methotrexate. - MATE1/MATE2-K/OCT transporter [c]: metformin.
Prevention or Management:	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.
Oral Drugs That Are Sensitive Substrates of CYP3A4	
Clinical Implication:	Xanomeline, a component of COBENFY, 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. This may increase the frequency and/or severity of adverse reactions from such substrates *[see Clinical Pharmacology (12.3)]*. Examples of sensitive substrates[d] for CYP3A4 include budesonide, aldenafil, isavuconazole, darunavir[g], indinavir[g], saquinavir[g], tipranavir[g], maraviroc, dasatinib, everolimus, ibrutinib, mobocertinib, sirolimus, venetoclax, felodipine, eplerenone, ivabradine, nisoldipine, ticagrelor, dronedarone, buspirone, lurasidone, quetiapine, lemborexant, midazolam, triazolam, avanafil, sildenafil, vardenafil, tacrolimus, , lovastatin, simvastatin, lomitapide, conivaptan, darifenacin, eletriptan, naloxegol, tolvaptan. Examples of moderate sensitive substrates[e] for CYP3A4 include alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban and tadalafil.
Prevention or Management:	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.
Oral Drugs That Are Substrates of P-glycoprotein	

Clinical Implication:	Xanomeline, a component of COBENFY, transiently inhibits P-glycoprotein locally in the gut but not systemically. Concomitant use of COBENFY with oral drugs that are substrates of P-glycoprotein may result in increased plasma concentrations of the oral drugs that are substrates of P-glycoprotein, which may increase the frequency and/or severity of adverse reactions from such substrates *[see Clinical Pharmacology (12.3)]*. Examples of clinical substrates[f] for P-gp include dabigatran etexilate, digoxin, edoxaban, and fexofenadine.
Prevention or Management:	Monitor patients for increased frequency and/or severity of adverse reactions related to oral drugs that are narrow therapeutic index substrates of P-glycoprotein in patients taking COBENFY with such substrates.

[a] Drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥ 5-fold

[b] Drugs with evidence of in vitro transport and AUC fold-increase ≥ 1.5 with probenecid co-administration and fraction of the dose excreted into urine as an unchanged drug ≥ 0.5

[c] Drugs with evidence of in vitro transport and AUC fold-increase ≥1.5 with dolutegravir or pyrimethamine co-administration and fraction of dose excreted into urine as an unchanged drug ≥0.5

[d] Drugs that demonstrate an increase in AUC of ≥ 5-fold with strong inhibitors of a given metabolic pathway.

[e] Drugs that demonstrate an increase in AUC of ≥ 2- to < 5-fold with strong inhibitors of a given metabolic pathway.

[f] Drugs with evidence of 1) in vitro transport; 2) not extensively metabolized in vivo; and AUC fold-increase ≥ 1.5 with itraconazole, verapamil or quinidine co-administration.

[g]Usually administered to patients in combination with ritonavir, a strong CYP3A4 inhibitor.

7.2 Other Antimuscarinic Drugs

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.

7.3 Effects on Absorption of 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on COBENFY use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia *(see Clinical Considerations)*. In animal reproduction studies, oral administration of xanomeline alone or in combination with trospium chloride during the period of organogenesis or during pregnancy and lactation caused maternal toxicities of adverse clinical signs, decreased body weight, weight gain and food consumption, and/or maternal death. At these maternally toxic doses, embryofetal and developmental toxicities included decreased fetal and neonatal weight, stillborn pups, and/or neonatal deaths. The no observed adverse effect level (NOAEL) of xanomeline or xanomeline/trospium chloride combination for maternal, embryofetal, and/or developmental

toxicity is equal to or higher than the xanomeline and trospium chloride dose at the maximum recommended human dose (MRHD) of 250/60 mg xanomeline/trospium chloride, based on mg/m^2 body surface area (BSA) *(see Data).*

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defect, loss, or other adverse outcomes.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk
There is a risk to the pregnant patient from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Data

Animal Data

Pregnant rats were orally treated during the period of organogenesis with 150 mg/kg/day xanomeline alone, 100 mg/kg/day trospium chloride alone, or xanomeline/trospium chloride combination at 30/25, 75/50, and 150/100 mg/kg/day, respectively. Xanomeline alone and the high dose combination caused maternal toxicities of decreased body weight, weight gain, and food consumption. At these maternally toxic doses, fetal weights were decreased. The NOAEL for maternal and embryofetal toxicity is 75/50 mg/kg/day for the combination, which is approximately 3 and 8 times the xanomeline and trospium chloride dose, respectively, at the MRHD of 250/60 mg xanomeline/trospium chloride, based on BSA. No fetal malformation was observed. Trospium chloride alone did not cause maternal or embryofetal toxicity.

Pregnant rabbits were orally treated during the period of organogenesis with120 mg/kg/day xanomeline alone, 80 mg/kg/day trospium chloride alone, or xanomeline/trospium chloride combination at 30/20, 60/40, and 120/80 mg/kg/day, respectively. Xanomeline alone and the high dose combination caused maternal toxicities of decreased body weight, weight gain, and food consumption, and/or early abortion. At these maternally toxic doses, decreased fetal weight and decreased fetal viability (increased resorption and post-implantation loss) were observed. The NOAEL for maternal and embryofetal toxicity is 60/40 mg/kg/day for the xanomeline/trospium chloride combination, which is 5 and 13 times the xanomeline and trospium chloride dose, respectively at the MRHD, based on BSA. No fetal malformation was observed. Trospium chloride alone did not cause maternal or embryofetal toxicity.

Rats were orally treated during pregnancy and lactation with 30, 75, and 150 mg/kg/day xanomeline alone, 100 mg/kg/day trospium chloride alone, or xanomeline/trospium chloride combination at 30/25, 75/50, and 150/100 mg/kg/day, respectively. Xanomeline alone at ≥ 75 mg/kg/day or in combination with trospium chloride at ≥ 75/50 mg/kg/day caused maternal toxicity of adverse clinical signs, decreased body weight, weight gain, food consumption, and maternal death. At these maternally toxic doses, developmental toxicity was observed in the offspring, including growth suppression (decreased body weight and weight gain), delayed

developmental landmarks, stillborn pups, and neonatal deaths. No drug effect was observed on the neurobehavioral function, including learning and memory, or the reproductive capacity of the offspring. The NOAEL for maternal and developmental toxicity is 30/25 mg/kg/day for the xanomeline/trospium chloride combination, which is approximately 1 and 4 times the xanomeline and trospium chloride dose, respectively at the MRHD, based on BSA. Trospium chloride alone did not cause maternal or developmental toxicity.

Pregnant rats were treated during the period of organogenesis with trospium chloride at doses up to 200 mg/kg/day. No malformation or fetal toxicity was observed up to 200 mg/kg/day, which is approximately 32 times the trospium chloride dose at the MRHD of 250/60 mg xanomeline/trospium chloride based on BSA.

Pregnant rabbits were treated during the period of organogenesis with trospium chloride at doses up to 200 mg/kg/day. Maternal toxicity (reduced feces, hunched posture, and diarrhea) was observed at 200 mg/kg/day. The NOAEL for maternal toxicity is 20 mg/kg/day, which is approximately 3 times the trospium chloride dose at the MRHD based on BSA.

Rats were orally treated during pregnancy and lactation with trospium chloride at doses up to 200 mg/kg/day. Maternal toxicity (death, irregular breathing, increased excitability) and neonatal deaths were observed at 200 mg/kg/day, which is approximately 32 times the MRHD, based on BSA. The NOAEL for maternal and developmental toxicity is 20 mg/kg/day, which is approximately 3 times the trospium chloride dose at the MRHD, based BSA.

8.2 Lactation

Risk Summary

There are no data on the presence of xanomeline or trospium in human milk, the effects on the breastfed infant, or the effects on milk production. Xanomeline and trospium are present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COBENFY and any potential adverse effects on the breastfed infant from COBENFY or from the underlying maternal condition.

8.4 Pediatric Use

Cobenfy is indicated for adults aged 18 years and older and it is not indicated for children. The safety and effectiveness of COBENFY in pediatric patients have not been established.

8.5 Geriatric Use

Controlled clinical studies of COBENFY did not include patients older than 65 years of age to determine whether they respond differently from younger adult patients.

Because COBENFY can increase the risk of urinary retention in geriatric patients, including older males with bladder outlet obstruction due to benign prostatic hyperplasia (BPH), a slower titration and lower maximum dosage is recommended in geriatric patients *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

8.6 Renal Impairment

Patients with mild renal impairment (eGFR 60 to <90 mL/min) showed higher systemic exposures to trospium chloride and xanomeline, the components of COBENFY, compared to subjects with normal renal function. However, in the adequate and well-controlled clinical studies, the safety profiles in patients with mild renal impairment were similar to those observed in patients with normal renal function (eGFR ≥90 mL/min). Therefore, the recommended dosage in patients with mild renal impairment is the same as the recommended dosage for patients with normal renal function.

Use of COBENFY is not recommended in patients with moderate or severe renal impairment (eGFR<60 mL/min) *[see Warnings and Precautions (5.1, 5.8) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Patients with mild to moderate hepatic impairment (Child-Pugh Class A and B, respectively) have higher xanomeline exposures compared to patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. The pharmacokinetics of COBENFY were not studied in patients with severe hepatic impairment (Child-Pugh Class C).

Use of COBENFY is contraindicated in patients moderate or severe hepatic impairment *[see Contraindications (4) and Warnings and Precautions (5.2)]*. It is not recommended in patients with mild hepatic impairment.

10 OVERDOSAGE

Overdose of COBENFY may produce cholinergic, anticholinergic or a combination of cholinergic and anticholinergic signs and symptoms:

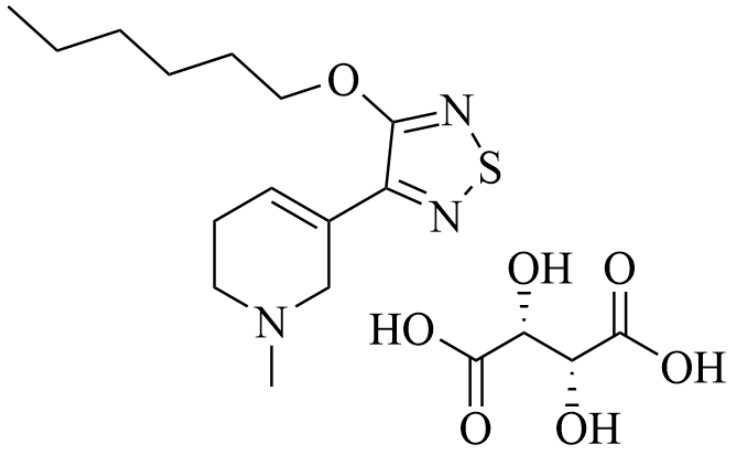
- Cholinergic Signs and Symptoms: seizures, vomiting, diarrhea, abdominal pain, hyperhidrosis, salivary hypersecretion, and hypotension possibly preceded by hypertension.
- Anticholinergic Signs and Symptoms (geriatric patients may be more susceptible): delirium, agitation, garbled speech, dizziness, hypertension, tachycardia, dry mouth and eyes, ileus, blurred vision, and urinary retention.

11 DESCRIPTION

COBENFY is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist.

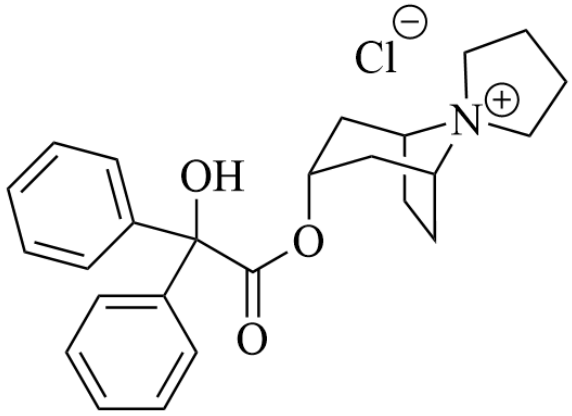
The chemical name of xanomeline tartrate is pyridine, 3-[4-(hexyloxy)-1,2,5-thiadiazol-3-yl]-1,2,5,6-tetrahydro-1-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1). Its molecular formula is $C_{14}H_{23}N_3OS.C_4H_6O_6$ and its molecular weight is 431.51 g/mol. Xanomeline tartrate is a white to slightly tan crystalline solid. Xanomeline tartrate is highly soluble in protic solvents, such as methanol and water, and in polar organic solvents such as DMF and dimethyl sulfoxide (DMSO). It is poorly soluble in lipophilic organic solvents, such as hexane or octanol.

The chemical structure of xanomeline tartrate is:



Trospium chloride is a quaternary ammonium compound with the chemical name of spiro[8-azoniabicyclo[3.2.1]octane-8,1′-pyrrolidinium], 3-[(2-hydroxy-2,2-diphenylacetyl)oxy]-, chloride (1:1), (1α,3β,5α). The molecular formula of trospium chloride is $C_{25}H_{30}NO_3.Cl$ and its molecular weight is 427.96 g/mol. Trospium chloride is a fine, colorless to slightly yellow, crystalline solid. Trospium chloride is highly soluble in water, freely soluble in methanol, and practically insoluble in methylene chloride.

The chemical structure of trospium chloride is:



COBENFY (xanomeline and trospium chloride) is for oral administration and is available in capsules in the following strengths:

- 50 mg/20 mg (equivalent to 76.7 mg xanomeline tartrate and 18.3 mg trospium).
- 100 mg/20 mg (equivalent to 153.3 mg xanomeline tartrate and 18.3 mg trospium).
- 125 mg/30 mg (equivalent to 191.7 mg xanomeline tartrate and 27.5 mg trospium).

COBENFY capsules contain a combination of pellets of xanomeline and pellets of trospium chloride.

Inactive ingredients: The xanomeline tartrate pellets contain microcrystalline cellulose, ascorbic acid and talc.

The trospium chloride pellets contain microcrystalline cellulose, lactose monohydrate and talc.

The capsules, printed with black ink, contain hypromellose, titanium dioxide, red iron oxide, black iron oxide (only 100 mg/20 mg) and yellow iron oxide (only 50 mg/20 mg and 100 mg/20 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of xanomeline in the treatment of schizophrenia is unclear; however, its efficacy is thought to be due to its agonist activity at M1 and M4 muscarinic acetylcholine receptors in the central nervous system.

Trospium chloride is a muscarinic antagonist. Trospium chloride antagonizes the muscarinic receptors primarily in the peripheral tissues.

12.2 Pharmacodynamics

Xanomeline binds to muscarinic receptors M1 to M5 with comparable affinity (Ki=10, 12, 17, 7, and 22 nM for the M1, M2, M3, M4, and M5 receptors, respectively) and exhibits higher agonist activity at the M1 and M4 receptors.

Trospium chloride antagonizes the muscarinic receptors primarily in peripheral tissues.

Cardiac Electrophysiology
At the maximum recommended dosage of 125 mg/30 mg twice daily, COBENFY does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Following COBENFY administration, xanomeline area under the plasma concentration-time curve during a 12-hour dosing interval (AUC_{0-12}) at steady state and maximum concentration (C_{max}) increased 50% when the COBENFY dose increased from 100 mg/20 mg twice daily to 125 mg/30 mg twice daily. Trospium exposures increase dose-proportionally over the COBENFY dosage range of 100 mg/20 mg twice daily to 125 mg/30 mg twice daily.

Pharmacokinetic properties of COBENFY are provided in Table 3.

Table 3: Pharmacokinetic Properties of COBENFY

Parameter		Xanomeline	Trospium
General Information			
Dose proportionality		Greater than proportional	Proportional
Accumulation[a]		2 to 3-fold	2 to 3-fold
Time to steady state		3 to 5 days	3 to 5 days
Absorption			
T_{max}		2 hours	1 hour
Effect of food: PK in fed state (compared to fasted state)			
High fat meal[b]	C_{max}	Unchanged	Reduced 70% to 75%
	AUC	Increased 30%	Reduced 85% to 90%
Low fat meal[b]	C_{max}	Unchanged	Reduced 70% to 75%
	AUC	Unchanged	Reduced 85% to 90%
Distribution			

Central volume of distribution (oral)		10,800 Liters	531 Liters
Plasma protein binding		Approximately 95%	Approximately 80%
Elimination			
Half-life ($t_{1/2}$)		5 hours	6 hours
Apparent clearance		1950 Liters/hour	796 Liters/hour
Renal clearance		0.085 Liters/hour	21 Liters/hour
Metabolism			
Primary metabolic pathways	CYP450	2D6, 2B6, 1A2, 2C9, and 2C19	Unlikely
	Other	Flavin monooxygenases (FMO1 and FMO3)	Ester hydrolysis and glucuronic acid conjugation (not fully characterized)
Excretion			
Urine	Total	78%	Unknown
	Unchanged	Less than 0.01%	85-90%
	Tubular secretion	Unknown	Yes
Feces	Total	12%	Unknown
	Unchanged	Unknown	Unknown

Abbreviations: AUC = Area under the time-concentration curve; C_{max} = Maximum concentration; T_{max} =Time to C_{max}

[a] Dose-normalized accumulation at steady state

[b] High-fat high-calorie meal is 800-1000 calories, 50% from fat; a low-fat meal is 400-500 calories, 25% from fat

Specific Populations

Geriatric Patients

Population pharmacokinetic analysis suggests that AUC_{0-12h} and C_{max} of trospium at steady state were 60% higher and 36% higher, respectively, in subjects 65 years and older compared to subjects younger than 65 years old. The exposures (AUC_{0-12h} and C_{max}) of xanomeline at steady state were not different between subjects 65 years and older and subjects younger than 65 years old *[see Dosage and Administration (2.3) and Use in Specific Populations (8.5)]*.

Male and Female Patients

Plasma concentrations of xanomeline and trospium are similar between females and males.

Racial or Ethnic Groups

Most subjects in clinical studies were Black.

Xanomeline and trospium exposure did not differ between Black and non-Black subjects. Studies have included too few subjects of Asian descent to evaluate comparisons.

Patients with Renal Impairment

The effect of renal impairment on xanomeline and trospium exposure was assessed in a dedicated study that enrolled healthy subjects and subjects with mild, moderate, or severe renal impairment. Estimated glomerular filtration rate (eGFR) was determined by the MDRD equation.

Plasma concentrations of xanomeline and trospium increased with increasing renal dysfunction *[see Use in Specific Populations (8.6)].* For xanomeline, compared to subjects with normal renal function (eGFR: ≥90 mL/min), the steady-state C_{max} and AUC_{0-12h} were 2.1 and 1.9 times higher in subjects with mild renal impairment (eGFR: 60 to <90 mL/min), 2.4 and 2.1 times higher in

subjects with moderate renal impairment (eGFR: 30 to <60 mL/min), and 2.6 and 2.4 times higher in subjects with severe renal impairment (eGFR: <30 mL/min). For trospium, compared to subjects with normal renal function, the steady-state C_{max} and AUC_{0-12h} were 1.6 and 1.6 times higher in subjects with mild renal impairment, 2.7 and 2.2 times higher in subjects with moderate renal impairment, and 2.9 and 2.9 times higher in subjects with severe renal impairment.

Patients with Hepatic Impairment
The effect of hepatic impairment on xanomeline and trospium in combination was assessed in a dedicated study that enrolled healthy subjects and subjects with mild or moderate hepatic impairment as determined by their Child-Pugh score.

Plasma concentrations of xanomeline increased with increasing hepatic dysfunction *[see Use in Specific Populations (8.7)].* In subjects with mild hepatic impairment (Child-Pugh Class A), the steady-state C_{max} and AUC_{0-12h} of xanomeline was 2.8 and 2.6 times that in subjects with normal hepatic function. Mild and moderate hepatic impairment did not substantially affect trospium exposure, but significantly impacted xanomeline exposures. In subjects with moderate hepatic impairment (Child-Pugh Class B), the steady-state C_{max} and AUC_{0-12h} of xanomeline was at least 7 times that in subjects with normal hepatic function *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

The effect of severe hepatic impairment on xanomeline and trospium exposure was not evaluated.

Body Weight
Compared to subjects weighing 70 kg, xanomeline exposures were 30 to 35% lower and trospium exposures were 20 to 35% lower in subjects weighing 120 kg. The lower exposures observed in subjects weighing 120 kg are expected to be clinically not meaningful.

Drug Interaction Studies

Drugs Eliminated by Active Tubular Secretion
Active tubular excretion is a major elimination pathway for trospium. Trospium has the potential for pharmacokinetic interactions with other drugs that are eliminated by active tubular secretion. Coadministration of COBENFY with these drugs may increase plasma concentrations of trospium and/or the coadministered drug due to competition for this elimination pathway *[see Drug Interactions (7.1)]*.

Metformin
A drug interaction study was conducted in which extended-release trospium chloride 60 mg once daily was coadministered with metformin hydrochloride 500 mg twice daily under steady-state conditions in 44 healthy subjects. Co-administration of 500 mg metformin immediate-release tablets twice daily reduced the steady-state systemic exposure of trospium by approximately 29% for mean AUC_{0-24} and by 34% for mean C_{max}. The steady-state pharmacokinetics of metformin were comparable when administered with or without 60 mg extended-release trospium chloride once daily under fasted conditions. The effect of metformin at higher doses on trospium pharmacokinetics is unknown.

Drugs That Inhibit CYP2D6
CYP2D6 is a significant contributor to the metabolism of xanomeline. Drugs that are inhibitors of CYP2D6 may increase xanomeline concentrations in plasma *[see Drug Interactions (7.1)].*

Drugs That Are Substrates of P-glycoprotein

In vitro data suggest that xanomeline does not inhibit P-glycoprotein systemically, but it may transiently inhibit P-glycoprotein locally in the intestine after dosing. COBENFY may increase plasma concentrations of coadministered P-gp substrates *[see Drug Interactions (7.1)]*.

Drugs That Are Substrates of CYP3A4
In vitro data suggest that xanomeline does not inhibit CYP3A4 systemically, but it may transiently inhibit CYP3A4 locally in the intestine after dosing. COBENFY may increase plasma concentrations of coadministered CYP3A4 substrates *[see Drug Interactions (7.1)]*.

12.5 Pharmacogenomics

CYP2D6 is a significant contributor to the metabolism of xanomeline. The gene encoding CYP2D6 has polymorphisms that impact protein function. Based on a population pharmacokinetic analysis, compared to subjects with normal CYP2D6 function, the median C_{max} and median AUC_{0-12h} of xanomeline were estimated to increase by 28% and 15% in CYP2D6 intermediate metabolizers (N=84) and decrease by 43% in both parameters for ultrarapid metabolizers (N=12)**.** The pharmacokinetics of xanomeline have not been adequately characterized in subjects who are poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Xanomeline
Xanomeline was administered to rats in the diet at doses of 9, 37, and 134 mg/kg/day in males and 11, 46, and 170 mg/kg/day in females, respectively, for two years. Biliary hyperplasia was observed in all groups with increased incidence and/or severity at ≥ 37 and 46 mg/kg/day in males and females, respectively, relative to controls. There was no increase in the incidence of tumors at doses up to 37 and 46/mg/kg/day in males and females, respectively; these doses are 1.4 to 1.8 times higher than the xanomeline dose at the MRHD of 250/60 mg xanomeline/trospium, based on mg/m^2 BSA. The high doses of 134 and 170 mg/kg/day in males and females exceeded the maximum tolerated dose (MTD), precluding an adequate assessment for carcinogenic effect at this dose.

Xanomeline was administered to mice in the diet at doses of 52, 174, and 559 mg/kg/day for 21 months in both sexes. Xanomeline did not increase the incidence of tumors in mice at doses up to 174 mg/kg/day, which is approximately 3 times the xanomeline dose at the MRHD, based on BSA. The high dose of 559 mg/kg/day exceeded the MTD, precluding an adequate assessment for carcinogenic effect at this dose.

Trospium chloride
Trospium chloride did not increase the incidence of tumors in rats treated for 104 weeks at doses up to 200 mg/kg/day, which is approximately 32 times the trospium chloride dose at the MRHD, based on BSA.

Trospium chloride did not increase the incidence of tumors in mice treated for 78 weeks at doses up to 200 mg/kg/day, which is approximately 16 times the trospium chloride dose at the MRHD, based on BSA.

Mutagenesis

Xanomeline
Xanomeline was not mutagenic in the in vitro bacterial reverse mutation (Ames assay) or mouse lymphoma assay. Xanomeline did not induce unscheduled DNA synthesis in rat hepatocytes and was not clastogenic in the in vitro chromosome aberration assay or in the in vivo mouse bone marrow micronucleus assay.

Trospium chloride
Trospium chloride was not mutagenic nor genotoxic in tests *in vitro* in bacteria (Ames assay) and mammalian cells (L5178Y mouse lymphoma and CHO cells) or *in vivo* in the rat micronucleus test.

Impairment of Fertility

Xanomeline
Xanomeline did not affect fertility when orally administered to male rats via the diet at doses of 15, 44, and 150 mg/kg/day. The NOAEL for male fertility is 150 mg/kg/day, which is approximately 6 times the xanomeline dose at the MRHD of 250/60 mg xanomeline/trospium, based on BSA.

Xanomeline did not affect fertility when administered subcutaneously to male and female rats at doses of 1, 5, and 25 mg/kg/day. The NOAEL for male and female fertility is 25 mg/kg/day, which is equal to the xanomeline dose at the MRHD, based on BSA.

Trospium chloride
Trospium chloride did not affect fertility in rats at doses up to 200 mg/kg/day which is approximately 32 times the trospium chloride dose at the MRHD, based on BSA.

13.2 Animal Toxicology and/or Pharmacology

In the 2-year dietary study in rats, biliary cysts and/or biliary/biliary ductule dilatation were observed at xanomeline doses equal to or greater than the MRHD of 250/60 mg xanomeline/trospium chloride, based on BSA.

14 CLINICAL STUDIES

The efficacy of COBENFY for the treatment of schizophrenia in adults was evaluated in two placebo-controlled studies with identical designs (N = 470). Study 1 (NCT04659161) and Study 2 (NCT04738123) were five-week, randomized, double-blind, placebo-controlled, multi-center studies in adult patients with a diagnosis of schizophrenia according to the DSM-5 criteria.

In Study 1 and Study 2, patients randomized to COBENFY were started on an initial dose of 50 mg/20 mg orally twice daily for the first 2 days and if tolerated, followed by 100 mg/20 mg orally twice daily for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing was titrated upwards to 125 mg/30 mg orally twice daily unless the patient could not tolerate it. All patients could return to 100 mg/20 mg orally twice daily for the remainder of the treatment period.

Demographic and baseline disease characteristics were similar for the COBENFY and placebo groups. Median age was 46 years (range 19 to 65 years). Twenty-five percent of patients were female, 31% were White, 68% were Black or African American, and 1% were Other (or not reported).

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 and Study 2, patients randomized to COBENFY showed a statistically significant reduction from baseline to Week 5 in the PANSS Total Score compared to the placebo group. The results of Studies 1 and 2 are shown in Table 4. 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.

Examination of subgroups by age, sex, and race did not suggest differences in response in the study (there were no patients over 65 years of age).

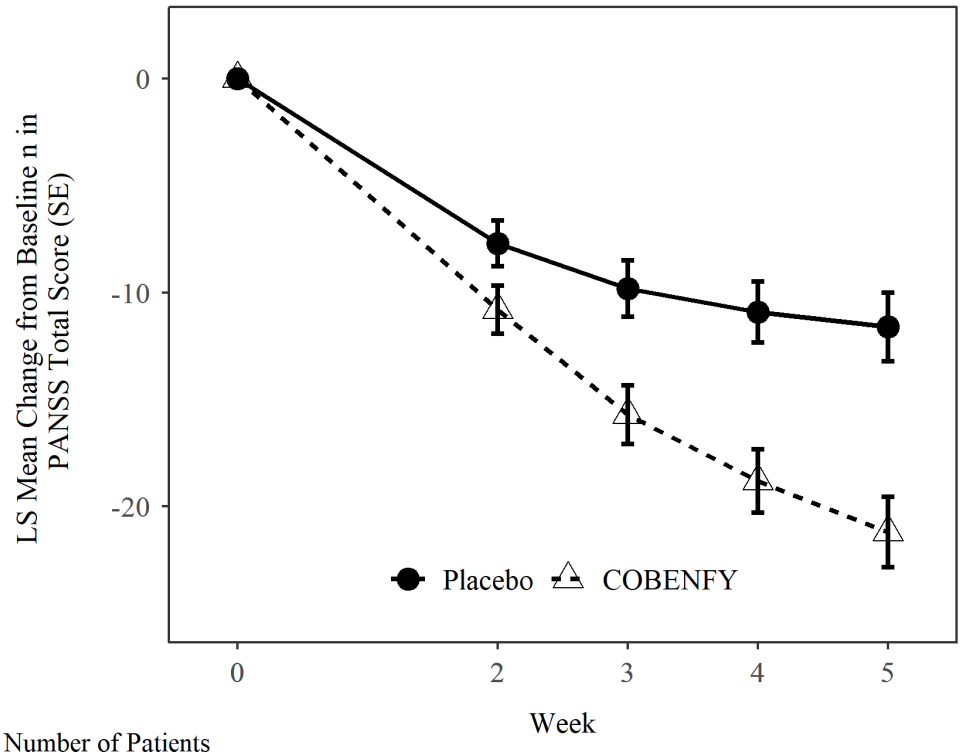
Table 4: Primary Efficacy Results for Change from Baseline in PANSS Total Score at Week 5 in Adults with Schizophrenia (Studies 1 and 2)

			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.

The change from baseline in PANSS total score to Week 5 is summarized in Figure 1.

Figure 1: Change from Baseline in PANSS Total Score by Week in Adults with Schizophrenia (Study 1)



Number of Patients					
Placebo:	119	115	106	103	99
COBENFY:	117	104	98	97	93

Error bars represent standard error. LS=least squares; SE=standard error

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

COBENFY is available as:

- 50 mg/20 mg (xanomeline/trospium chloride): Buff capsules imprinted with Karuna 50/20 mg
- 100 mg/20 mg (xanomeline/trospium chloride): Brown capsules imprinted with Karuna 100/20 mg
- 125 mg/30 mg (xanomeline/trospium chloride): Swedish Orange capsules imprinted with Karuna 125/30 mg

COBENFY capsules are packaged as described in Table 5.

Table 5: COBENFY Packaging Configurations

Capsule Strength	Total Package Count	Package Configuration
50 mg/20 mg	60	Bottle
100 mg/20 mg	60	Bottle
125 mg/30 mg	60	Bottle
50 mg/20 mg (4) 100 mg/20 mg (52)	56	Starter Pack for 100 mg/20 mg dose
50 mg/20 mg	56	Blisters
100 mg/20 mg	56	Blisters
125 mg/30 mg	56	Blisters

Not all packaging configurations are marketed.

Storage and Handling

Do not store above 25°C.

The expiry date of the product is indicated on the packaging materials.

Shelf life after opening the bottle package:

6 months. Do not store above 25°C.

17 MANUFACTURER

Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08453, USA

18 REGISTRATION HOLDER

Bristol-Myers Squibb Israel Ltd., 18 Aharon Bart St., Kiryat Arye, Petah-Tikva 4951448, Israel

19 REGISTRATION NUMBER

180-58-38381

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