U.S. Food and Drug Administration Approves Bristol Myers Squibb's COBENFY™ (xanomeline and trospium chloride), a First-In-Class Muscarinic Agonist for the Treatment of Schizophrenia in Adults

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PRINCETON, N.J.--(BUSINESS WIRE)--Bristol Myers Squibb (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved COBENFY™ (xanomeline and trospium chloride), an oral medication for the treatment of schizophrenia in adults.[1] COBENFY represents the first new class of medicine in several decades and introduces a fundamentally new approach to treating schizophrenia by selectively targeting M_1 and M_4 receptors in the brain without blocking D_2 receptors.[2,3,4]

Product Image (Photo: Bristol Myers Squibb)

"Today's landmark approval of our first-in-class treatment for schizophrenia marks an important milestone for the community, where after more than 30 years, there is now an entirely new pharmacological approach for schizophrenia — one that has the potential to change the treatment paradigm," said Chris Boerner, PhD, board chair and chief executive officer at Bristol Myers Squibb. "As we reenter the field of neuropsychiatry, we are dedicated to changing the conversation around serious mental illness, beginning with today's approval in schizophrenia."

Schizophrenia is a persistent and often disabling mental illness affecting how a person thinks, feels and behaves.[5] It is estimated to impact approximately 2.8 million people in the United States.[6] Symptoms typically first appear in early adulthood and present differently in each person, making symptoms difficult to diagnose and manage.[6] While the current standard of care can be effective in managing symptoms of schizophrenia, up to 60% of people experience inadequate improvement in symptoms or intolerable side effects during therapy.[7]

"For people living with schizophrenia, it's often difficult to find a treatment that works for them. Having a variety of treatment options gives patients and healthcare providers the tools to help manage this serious condition," said Gordon Lavigne, chief executive officer of the Schizophrenia & Psychosis Action Alliance. "People living with schizophrenia want and deserve more. Today's approval provides a new option as people with schizophrenia move forward with proper support to rebuild their lives."

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. In the Phase 3 EMERGENT-2 and EMERGENT-3 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) total score change from baseline to week five. COBENFY demonstrated a 9.6-point reduction (-21.2 COBENFY vs. -11.6 placebo, $p<0.0001$) and an 8.4-point reduction (-20.6 COBENFY vs. -12.2 placebo; $p<0.0001$) in PANSS total score compared to placebo at week five in EMERGENT-2 and EMERGENT-3, respectively. In EMERGENT-2, COBENFY demonstrated a statistically significant improvement in illness from baseline to week five, as measured by the Clinical Global Impression-Severity (CGI-S) score, a secondary endpoint in the trial.[1]

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) were nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness and gastroesophageal reflux disease.[1] COBENFY does not have atypical antipsychotic class warnings and precautions and does not have a boxed warning.

"Due to its heterogeneous nature, schizophrenia is not a one-size-fits-all condition, and people often find themselves in a cycle of discontinuing and switching therapies," said Rishi Kakar, MD, chief scientific officer and medical director at Segal Trials and investigator in the EMERGENT program. "The approval of COBENFY is a transformative moment in the treatment of schizophrenia because, historically, medicines approved to treat schizophrenia have relied on the same primary pathways in the brain. By leveraging a novel pathway, COBENFY offers a new option to manage this challenging condition."

The Company today also announced the launch of COBENFY Cares™, a program designed to support patients who have been prescribed COBENFY. Patients will be able to enroll in the COBENFY Cares program in late October corresponding with product availability. The COBENFY Cares phone number is 1-877-COBENFY.

About Schizophrenia

Schizophrenia is a persistent and often disabling mental illness impacting how a person thinks, feels and behaves. There are three symptom domains of schizophrenia, which include positive symptoms (e.g., hallucinations, delusions, disordered thinking and speech), negative symptoms (e.g., lack of motivation, lack of emotional expression/flat affect, social withdrawal) and cognitive dysfunction (e.g., impaired attention, deficits in memory, concentration and decision-making).[5] The symptoms of schizophrenia can affect all areas of people's lives, making it difficult to maintain employment, live independently and manage relationships.[8,9] Schizophrenia affects nearly 24 million people worldwide, including 2.8 million people in the United States, and is one of the top 15 leading causes of disability worldwide.[6,10,11]

About COBENFY™ (xanomeline and trospium chloride)

COBENFY™ (xanomeline and trospium chloride), formerly KarXT, is an oral medication for the treatment of schizophrenia in adults. 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. 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.

About EMERGENT Clinical Program

The EMERGENT clinical program evaluating COBENFY for the treatment of schizophrenia in adults includes three placebo-controlled efficacy and safety studies, including the Phase 3 EMERGENT-2 and EMERGENT-3 trials, and two open-label studies 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) total score change from baseline to week five.

COBENFY demonstrated a 9.6-point reduction (-21.2 COBENFY vs. -11.6 placebo, $p<0.0001$) and an 8.4-point reduction (-20.6 COBENFY vs. -12.2 placebo; $p<0.0001$) in PANSS total score compared to placebo at week five in EMERGENT-2 and EMERGENT-3, respectively. 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 compared to placebo at week five, a secondary endpoint in the trial.

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%).

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.

Increases 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.

About Bristol Myers Squibb

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube, Facebook and Instagram.

Cautionary Statement Regarding Forward-Looking Statements

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, whether COBENFY (xanomeline and trospium chloride) for the indication described in this release will be commercially successful, any marketing approvals, if granted, may have significant limitations on their use, and that continued approval of COBENFY for such indication described in this release may be contingent upon verification and description of clinical benefit in confirmatory trials. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb’s business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2023, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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