Category

Best Pharmaceutical Product

General Information

Company Name *

Bristol Myers Squibb

Product/Solution Name *

Cobenfy

Compound/Tech Name*

xanomeline and trospium chloride

Trade Name *

Cobenfy

Corporate Name *

Cobenfy

Date of Approval *

2024-09-26

Indications *

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

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482

Therapeutic Areas *

Cobenfy is a combination of a muscarinic agonist and a muscarinic antagonist approved by the U.S. FDA for the treatment of schizophrenia in adults.

words remaining :

476

*Kindly clearly label your files with company name and asset name.

Attached Files:

- Bristol Myers Squibb_Cobenfy_PI.pdf

Background information and need for drug / device
(please be as specific as possible in your description; limit 500 words)

Neuropsychiatric conditions like schizophrenia are inherently complex and represent some of the greatest challenges of our time. With limited understanding of the etiology of many psychiatric diseases, the last several decades have relied on serendipity to fuel innovation.

The first antidepressant (iproniazid) was originally an antibiotic intended to treat tuberculosis, and the first antipsychotic (chlorpromazine) came from an attempt by a surgeon to look for better tranquilizers - both of which spurred decades of research and development, producing several classes of medicines that are still used today.

While the role of acetylcholine was thought to be part of the underlying etiology of psychosis, most drug development was directed toward dopamine receptor antagonists - enter xanomeline, a dual M1- and M4-preferring muscarinic acetylcholine receptor agonist. The idea behind xanomeline for the treatment of psychotic symptoms was discovered because of an Eli Lilly program in the 1990s evaluating the compound for the treatment of cognitive decline in Alzheimer's disease. However, it was shelved due to its side effects despite years of development.

In 2009, a visionary team at Puretech, consisting of Andrew Miller, Eric Elenko, and Philip E. Murray, embarked on a journey that would lead to a groundbreaking advancement in neuropsychiatric treatment. Inspired by the 1997 publication from Eli Lilly showcasing the antipsychotic potential of xanomeline, they conceived an innovative approach to enhance its therapeutic benefits while minimizing side effects. Their idea was to pair xanomeline with another compound that could counterbalance its adverse effects without compromising its brain-penetrant potency.

Through meticulous research and experimentation with thousands of combinations, the team discovered a promising partner in an overactive bladder medication known as trospium. This pairing laid the foundation for the development of KarXT (xanomeline and trospium chloride), a novel therapeutic solution that offers significant advancement in treating psychiatric disorders.

Karuna Therapeutics, a Puretech spin-off subsequently acquired by Bristol Myers Squibb, continued to drive this innovation forward by developing the formulations, devising the dosing regimens, and conducting all necessary clinical trials. This steadfast dedication and comprehensive research process culminated in the creation of the revolutionary medication now known as Cobenfy. Moreover, Karuna holds an exclusive license to the Puretech patent, solidifying its role in this transformative development.

The development of Cobenfy underscores a remarkable leap forward in psychiatric treatment, combining scientific insight with therapeutic efficacy.

Prior to the approval of Cobenfy, medicines approved to treat adults with schizophrenia have relied on blocking the dopaminergic receptors in the brain. Typical antipsychotics (e.g., haloperidol) are characterized by their exclusive blockade of the D2 receptor. Atypical antipsychotics target dopamine along with other receptors and share similar side effects and warnings as typical antipsychotics due to overlapping pharmacology. Both classes have a black boxed warning for the risk of increased mortality in elderly patients with dementia-related psychosis.

words remaining :

39

*Kindly clearly label your files with company name and asset name.

Attached Files:

- Bristol Myers Squibb_Cobenfy_Karuna Acquisition Announcement Press Release.pdf
- Bristol Myers Squibb_Cobenfy_Karuna Acquisition Close Press Release.pdf
- Bristol Myers Squibb_Cobenfy_Clozapine as a model for antipsychotic development.pdf
- Bristol Myers Squibb_Cobenfy_First Generation Versus Second Generation Antipsychotics in Adults.pdf
- Bristol Myers Squibb_Cobenfy_Bodick et al 1997.pdf

**History of the development of the solution/product *
(please be as specific as possible in your description; 500 words)**

The efficacy, safety and tolerability of Cobenfy has been established across four acute (5 week) and two long-term (52 week) clinical trials as part of the global EMERGENT program. In all placebo-controlled clinical trials, Cobenfy demonstrated statistically significant and clinically relevant reductions in overall schizophrenia symptoms and across symptom domains, including positive, negative and cognitive, compared to placebo as measured by the Positive and Negative Syndrome Scale (PANSS) total score.

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.

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. Nausea and vomiting often occurred during the first two weeks of treatment and generally decreased over time. Across acute and long-term trials, Cobenfy had a low incidence of weight gain, metabolic changes and movement disorders. Cobenfy is contraindicated in patients with urinary retention, moderate or severe hepatic impairment, gastric retention, history of hypersensitivity to Cobenfy or trospium chloride, and untreated narrow-angle glaucoma. Cobenfy does not have atypical antipsychotic class warnings and precautions and does not have a boxed warning.

Data from EMERGENT has been published in the New England Journal of Medicine, The Lancet, and JAMA Psychiatry.

The U.S. FDA approved Cobenfy for the treatment of schizophrenia in adults in September 2024.

While the current standard of care can be effective in managing symptoms of schizophrenia, studies have shown that approximately 40% of people do not respond to therapy, and up to 60% experience a partial or inadequate improvement or intolerable side effects during therapy. In a long-term NIMH study, approximately 75% of patients discontinued treatment within the first 18 months, with many failing to find an effective and/or tolerable therapy. Side effects from existing antipsychotics can include motor disturbances (e.g., tremors), sedation, vision impairments, seizures, and neuroleptic malignant syndrome. Similarly, atypical antipsychotics are associated with significant weight gain, hyperlipidemia, insulin resistance/diabetes, QTc prolongation, extrapyramidal symptoms (EPS), tardive dyskinesia, and sexual dysfunction due to prolactin elevation.

For the last 70 years, people living with schizophrenia have essentially been treated with a single class of medication - Cobenfy introduces the first medication with a novel mechanism of action in decades.

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Attached Files:

- Bristol Myers Squibb_Cobenfy_FDA Issued Press Release.pdf
- Bristol Myers Squibb_Cobenfy_US FDA Approval Press Release.pdf
- Bristol Myers Squibb_Cobenfy_Zai Lab Phase 3 Study Press Release.pdf
- Bristol Myers Squibb_Cobenfy_PI.pdf
- Bristol Myers Squibb_Cobenfy_JAMA Psychiatry EMERGENT3 Publication.pdf
- Bristol Myers Squibb_Cobenfy_GBD 2016 Disease Burden.pdf
- Bristol Myers Squibb_Cobenfy_Atypical Treatment Switches in Schizophrenia.pdf
- Bristol Myers Squibb_Cobenfy_Schizophrenia Overview and Treatment Options_PT.pdf
- Bristol Myers Squibb_Cobenfy_Treatment Resistance in Schizophrenia_Braz J Psychiatry.pdf
- Bristol Myers Squibb_Cobenfy_NEJM EMERGENT1 Publication.pdf
- Bristol Myers Squibb_Cobenfy_Lancet EMERGENT2 Publication.pdf

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition *

Cobenfy is the first differentiated mechanism of action to treat schizophrenia in decades, activating muscarinic receptors as opposed to targeting dopamine receptors, which has long been the standard of care. This novel mechanism marks a significant breakthrough in schizophrenia treatment, offering a fresh approach after decades of limited innovation in the field.

Cobenfy is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist, indicated for the treatment of schizophrenia in adults. 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 antagonizes the muscarinic receptors primarily in the peripheral tissues and does not measurably cross the blood brain barrier, which helps to improve tolerability.

In contrast, typical antipsychotics mainly antagonize dopamine receptors while atypical antipsychotics can act as partial agonists or antagonists at dopamine and serotonin receptors. Until recently, schizophrenia has been mainly treated as a disease of dopamine dysfunction with the important role of acetylcholine and its receptors having been under-investigated for decades.

Cobenfy's unique mechanism of action, coupled with its robust efficacy and demonstrated side effect profile position it as a treatment option for adult patients living with schizophrenia.

Cobenfy is being evaluated in other neuropsychiatric indications in which acetylcholine is thought to play a role in the underlying mechanism of disease, including psychosis in Alzheimer's disease,

Alzheimer's disease agitation, Alzheimer's disease cognition impairment, bipolar disorder-mania/mixed features, and autism spectrum disorder-related irritability.

Like many serendipitous findings before, we believe that the development of muscarinic agonists will spur another wave of innovation for the treatment of behavioral and psychiatric disorders, and a renaissance in psychiatry research - a population with an urgent need for new treatment options.

Cobenfy was included on TIME's Best Inventions of 2024, referred to as a "game changer" by the Washington Post, and received extensive coverage from the New York Times, Wall Street Journal and others.

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- Bristol Myers Squibb_Cobenfy_PI.pdf
- Bristol Myers Squibb_Cobenfy_Clozapine as a model for antipsychotic development.pdf
- Bristol Myers Squibb_Cobenfy_First Generation Versus Second Generation Antipsychotics in Adults.pdf

Please provide appropriate references (PubMed, Abstract, Website) *

References included throughout submission; hyperlinks included below to related media coverage.

The New York Times: https://www.nytimes.com/2024/09/26/health/fda-schizophrenia-drug.html

TIME: https://time.com/7094904/bristol-myers-squibb-cobenfy/

Washington Post: https://www.washingtonpost.com/business/2024/09/26/fda-antipsychotic-mental-illness-alzheimers/

The Wall Street Journal: https://www.wsj.com/health/pharma/first-novel-schizophrenia-treatment-in-decades-gains-fda-approval-730813e8?msockid=0b6efd53636c61be27d9e9e562f56041

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