

**Company**

Alkermes, Inc

**Drug or Device Name**

LYBALVI®

**Category**

Pharmaceutical

**Compound/Technical Name**

olanzapine and samidorphan (OLZ/SAM)

**Trade Name**

LYBALVI®

**Date of Approval**

05/28/2021

**Therapeutic Categories**

Schizophrenia and bipolar 1 disorder

**Indications**

Schizophrenia and bipolar 1 disorder are chronic mental illnesses with significant impact on patients' lives. Schizophrenia is characterized by disordered thought processes and behavior, positive symptoms (e.g. hallucinations, delusions) and negative symptoms (e.g. apathy, diminished emotional expression), as well as cognitive impairment.(1) Estimates of the 12-month prevalence of schizophrenia and related psychotic disorders in the United States (US) population range between 0.25% and 1.1%.(2-5) Symptoms of schizophrenia generally emerge in late adolescence or early adulthood, altering the course of patients' lives. Bipolar 1 disorder is characterized by manic episodes with many patients also experiencing depressive episodes.(1) The 12-month prevalence estimates of adults with bipolar 1 disorder in the US range from 0.6% to 2.0%.(6-8) Both disorders are associated with substantial psychosocial disability, high rates of comorbid psychiatric conditions, a greater need for mental healthcare services, and high risk of suicide. The coronavirus pandemic has resulted in a disproportionate burden for people affected by schizophrenia or bipolar 1 disorder.(9-10) LYBALVI® is a treatment that helps adults living with schizophrenia or bipolar 1 disorder. LYBALVI, an oral prescription medication, is a combination of olanzapine, an atypical antipsychotic, and samidorphan, an opioid antagonist, indicated for the treatment of schizophrenia in adults and bipolar 1 disorder in adults as an acute treatment of manic or mixed episodes as monotherapy and as an adjunct to lithium or valproate and as maintenance monotherapy treatment.(11)

**Background**

Antipsychotics, the class of medications commonly used to treat patients with schizophrenia or bipolar 1 disorder, control the symptoms of the underlying disorder and patients typically require life-long

treatment to prevent recurrence of symptoms.(12-15) While there are a number of approved antipsychotics, response to any one antipsychotic cannot easily be predicted and clinicians must individually tailor the treatments that optimally balance efficacy, safety and tolerability for patients. The goal of treatment is to reduce symptoms and increase functionality. The current treatment paradigm, however, often forces clinicians and patients to make a difficult choice between efficacy and tolerability. Olanzapine was originally approved under the brand name Zyprexa® in 1996 (16) and is widely considered one of the most efficacious antipsychotics for the treatment of schizophrenia and bipolar I disorder, as demonstrated by lower rates of hospitalization for disease exacerbation, higher rates of remission, and longer time to all-cause discontinuation compared to most antipsychotics. (17-26) However, significant weight gain and metabolic effects associated with olanzapine has severely limited its clinical utility.(27-28) Weight gain often occurs early, continues to increase over time and persists for years.(29) Weight gain thus presents a long-term safety risk to patients and is a significant factor to consider when clinicians decide whether to prescribe olanzapine. Weight gain may also have a profound impact on patient's lives including psychosocial adaptation, body image, and self-esteem. (30-34) The increased prevalence of cardiometabolic comorbidities in patients with schizophrenia and bipolar I disorder ultimately leads to increased mortality.(35-39) The life expectancy for individuals with schizophrenia or bipolar disorder is substantially decreased in comparison to the general population.

## Development

Numerous studies over the past twenty years have attempted to address olanzapine-associated weight gain through approaches such as pharmacological treatments and lifestyle interventions, with mixed results.(40) The ability to quickly pivot and develop new hypotheses is a mark of true innovation in drug development, such is the story for OLZ/SAM. A foundation of literature began to emerge that demonstrated that opioid receptor antagonists (also known as opioid receptor blockers) play a role in regulating weight and metabolism, potentially through mechanisms involving food reward and modulation of insulin sensitivity.(41) Samidorphan is an opioid antagonist with unique pharmacodynamic and pharmacokinetic properties discovered in the laboratory of Mark Wentland, a medicinal chemist and a professor emeritus of chemistry and chemical biology at Rensselaer Polytechnic Institute.(42) Exemplifying the importance of academic and industry collaboration in advancing drug development, Alkermes licensed samidorphan from Rensselaer in 2006. Alkermes has well-established expertise in opioid receptor antagonism in the field of addiction and originally intended to evaluate the novel opioid antagonist for the treatment of substance use disorders. During development, a potential effect of samidorphan on weight gain in animal models was observed and a new hypothesis emerged. Combining samidorphan and olanzapine was an innovative approach to a longstanding unmet need in the field of psychiatry. Alkermes submitted an Investigational New Drug (IND) application for OLZ/SAM on February 15, 2012. The clinical development program was composed of 27 clinical studies, including 18 conducted with OLZ/SAM and 9 with samidorphan alone. Overall, the safety profile of OLZ/SAM is now well understood and there is comparable antipsychotic efficacy and less weight gain with OLZ/SAM relative to olanzapine. OLZ/SAM received overwhelmingly positive endorsement from a US Food and Drug Administration (FDA) Advisory Committee composed of scientific experts on October 9, 2020 and FDA approval on May 28, 2021.

## Innovation

The submission of this application coincides with National Mental Health Awareness Month, an important opportunity to raise awareness and reduce stigma for the millions of people affected by mental illness. While we know that much more needs to be done to meet the needs of people living with serious mental illness, innovation in treatment unfortunately lags many other areas of medicine.

LYBALVI is the only new medication for the treatment of schizophrenia or bipolar I disorder approved since 2019. Meanwhile, these illnesses are chronic, debilitating, and are associated with substantial psychosocial disability, high rates of comorbid psychiatric conditions, a greater need for mental healthcare services, and high risk of suicide. In addition, the impacts go far beyond the individual, often significantly impacting families and even communities at large. Despite the availability of older FDA-approved medicines, these diseases are inadequately treated and are associated with enormous human burden and economic cost. Weight gain represents one of the key safety risks of olanzapine and has limited its use and utility, despite being a highly effective antipsychotic. Antipsychotic-associated weight gain can have a profound negative impact on patients' lives and is linked to serious health concerns, including premature mortality. The development program for LYBALVI sought to enhance the safety of olanzapine by mitigating olanzapine-associated weight gain with the addition of samidorphan, thus attempting to address a challenge faced by the field of psychiatry for decades. Focusing efforts on a new mechanism while leveraging a body of literature to support our hypothesis has led to the development of LYBALVI, a treatment that has been shown to offer the efficacy of olanzapine while mitigating its weight gain, one of its central liabilities. LYBALVI offers a new treatment option for patients.

## Pubmed

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double-blind, placebo-controlled proof of concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers. Silverman BL, Martin W, Memisoglu A, DiPetrillo L, Correll CU, Kane JM. Schizophr Res. 2018 May;195:245-251. doi: 10.1016/j.schres.2017.10.014. Epub 2017 Nov 20. PMID: 29158012 Clinical Trial.

#### Attachments

- 1655831513Alkermes\_Announces\_FDA\_Approval\_of\_LYBALVI\_press\_release.pdf
- 1655831528Alkermes\_Announces\_Commercial\_Availability\_of\_LYBALVI\_press\_release.pdf
- 1655928496Correll\_Am\_J\_Psych.2020\_A303.pdf
- 1655928507Kahn\_Schizophrenia\_Research\_A304\_published\_manuscript.pdf
- 1655928521J\_Clin\_Psychiatry\_2020\_Potkin\_A305\_Primary.pdf

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