NEW DRUG APPROVAL

Brand Name	Lybalvi™
Generic Name	olanzapine and samidorphan
Drug Manufacturer	Alkermes, Inc.

New Drug Approval

FDA Approval Date: May 28, 2021
Review Designation: Standard Review designation
Review Type: Type 1 - New Molecular Entity and Type 4 - New Combination; New Drug Application (NDA): 213378
Dispensing Restrictions: Open distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Schizophrenia is a is a chronic and severe neurological brain disorder marked by positive symptoms (hallucinations and delusions, disorganized speech and thoughts, and agitated or repeated movements) and negative symptoms (depression, blunted emotions and social withdrawal). Schizophrenia affects approximately 1.1% of the U.S. population. It was estimated in 2014 that it affects 1.1 percent of the population or approximately 2.6 million adults in the United States aged 18 or older. An estimated 40 percent of individuals with the condition are untreated in any given year.

Bipolar disorder is a brain disorder that is marked by extreme changes in a person's mood, energy, and ability to function. Individuals with this brain disorder may experience debilitating changes in mood from extreme highs (mania) to extreme lows (depression). Bipolar I disorder is characterized by the occurrence of at least one manic episode, with or without the occurrence of a major depressive episode and affects approximately one percent of the adult population in the United States in any given year.

The U.S. prevalence of schizophrenia has been estimated between 0.25% and 0.64% and for bipolar I disorder approximately 1%.

Efficacy

1. Schizophrenia

The approval of Lybalvi™ was based on two Phase 3 trials: Enlighten-1 and Enlighten-2. The purpose of Enlighten-1 was to ensure that the addition of samidorphan would not alter the known antipsychotic efficacy of olanzapine. The Enlighten clinical trial program specifically assessed Lybalvi™ in the schizophrenia population.

Enlighten-1 was a 4-week, randomized, double-blind, placebo- and active-controlled Phase 3 trial in patients with schizophrenia. Patients were randomized 1:1:1 to receive Lybalvi™, olanzapine, or placebo. Patients could receive up to 20 mg of olanzapine in both arms. The primary efficacy endpoint was the change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at Week 4. The PANSS scale measures the various symptoms of schizophrenia, with a higher score equating to greater symptom severity. Patients in both the Lybalvi™ and olanzapine group experienced a statistically significant improvement in PANSS total score at Week 4 versus placebo. The results demonstrated that the addition of samidorphan did not alter the antipsychotic efficacy of olanzapine.

Study 1 (ENLIGHTEN-1; NCT02634346) Results		
Treatment Group	**Total PANSS Score**	
	LS Mean Change from Baseline	**Placebo-Subtracted Difference (95% CI)**
Lybalvi™ (N = 132)	–23.9	-6.4 (-10.0, -2.8)
Placebo (N = 133)	-17.5	-
Olanzapine (N = 132)	-22.8	-5.3 (-8.9, -1.7)

The purpose of Enlighten-2 was to compare the metabolic effects of Lybalvi™ versus olanzapine alone. Enlighten-2 was a 24-week, randomized Phase 3 trial that evaluated weight changes in patients with schizophrenia.

Study 2 (ENLIGHTEN-2; NCT02694328) Study Design	
Study Population	**Key inclusion criteria**: • Age 18–55 years • Meets DSM-5 criteria for a primary diagnosis of schizophrenia • Naïve to antipsychotic medication • BMI between 18 and 30 kg/m2 • Stable body weight (self-reported change <5%) for at least 3 months before study initiation **Key exclusion criteria**: • Naïve to antipsychotic medication • Active alcohol or substance use disorder (excluding marijuana) • Any clinically significant or unstable medical illness (e.g. diabetes) • Opioid agonist use within 14 days of screening • Opioid antagonist use within 60 days of screening • Use of olanzapine in the 60 days before screening All baseline characteristics were similar across the treatment arms, with a mean body weight of 77.17 kg (BMI: 25.38 kg/m^2) in the Lybalvi™ arm and 77.57 kg in the olanzapine arm (BMI: 25.52 kg/m^2).
Interventions	• Patients randomized 1:1 to receive Lybalvi™ or olanzapine • The daily doses consisted of 10 mg of samidorphan and either 10 mg or 20 mg of olanzapine, representing the highest and lowest approved maintenance dosages for schizophrenia

Endpoints	• Co-primary endpoints: ○ Percent change from baseline in body weight. ○ Proportion of patients who gained ≥ 10% of body weight at Week 24 • Key secondary endpoint: ○ Proportion of patients with ≥7% weight gain at Week 24

Abbreviations: BMI, body mass index; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

Study 2 (ENLIGHTEN-2; NCT02694328) Results							
Treatment Group	**% Change from Baseline in Body Weight**			**≥10% Body Weight Gain**		**≥7% Body Weight Gain[1]**	
	Baseline Mean, Kg	**LS Mean % Change From Baseline**	**Difference Versus Olanzapine (95% CI)**	**% of Patients**	**Difference Versus Olanzapine (95% CI)**	**% of Patients**	**Difference Versus Olanzapine (95% CI)**
Lybalvi™ (N = 266)	77.0	4.2	–2.4 (–3.9, –0.9)	17.8%	–13.7% (–22.8, –4.6)	27.5%	–15.2%
Olanzapine (N = 272)	77.5	6.6		29.8%		42.7%	

Abbreviations: CI, confidence interval; Derived from ENLIGHTEN-2 publication; 95% CI not provided

2. Bipolar I Disorder

Efficacy of Lybalvi™ for the bipolar I indication was based on previously reported literature for olanzapine monotherapy.

Monotherapy: The efficacy of oral olanzapine in the treatment of manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled studies in adult patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes.

These studies included patients with or without psychotic features and with or without a rapid-cycling course. The primary rating instrument used for assessing manic symptoms in these studies was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score).

In one 3-week placebo-controlled study (n=67) which involved a dose range of olanzapine (5 mg/day to 20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed study conducted simultaneously with the first study olanzapine demonstrated a similar treatment difference but, possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome. In a 4-week placebo-controlled study (n=115) which involved a dose range of olanzapine (5 mg/day to 20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

Adjunct to Lithium or Valproate: The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in 2 controlled studies in patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes.

In one 6-week placebo-controlled combination study, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5 mg/day to 20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

In a second 6-week placebo-controlled combination study, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5 mg/day to 20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

Safety

ADVERSE EVENTS

Most common adverse reactions (incidence ≥ 5% and at least twice placebo):

- Schizophrenia (Lybalvi™): weight increased, somnolence, dry mouth, and headache.
- Bipolar I Disorder, Manic or Mixed Episodes (olanzapine): asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor.
- Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine): dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia.

WARNINGS & PRECAUTIONS

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities).
- Precipitation of Opioid Withdrawal in Patients Who are Dependent on Opioids: LYBALVI can precipitate opioid withdrawal in patients who are dependent on opioids. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids to avoid precipitation of opioid withdrawal.
- Vulnerability to Life-Threatening Opioid Overdose:
  - Risk of Opioid Overdose from Attempts to Overcome LYBALVI Opioid Blockade: Attempts to overcome LYBALVI opioid blockade with high or repeated doses of opioids may lead to fatal opioid intoxication, particularly if LYBALVI therapy is interrupted or discontinued.
  - Risk of Resuming Opioids in Patients with Prior Opioid Use: Patients with a history of chronic opioid use prior to LYBALVI treatment may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued.
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue if DRESS is suspected.
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain.
- Tardive Dyskinesia: Discontinue if clinically appropriate.

- Orthostatic Hypotension and Syncope: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope.
- Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors.
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.
- Potential for Cognitive and Motor Impairment: Use caution when operating machinery.
- Anticholinergic (Antimuscarinic) Effects: Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions.
- Hyperprolactinemia: May elevate prolactin levels.
- Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, olanzapine, a component of Lybalvi™, elevates prolactin levels, and the elevation can persist during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary 10 gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

CONTRAINDICATIONS

- Patients using opioids.
- Patients undergoing acute opioid withdrawal.
- If Lybalvi™ is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for those products.

Clinical Pharmacology

MECHANISMS OF ACTION

The mechanism of action of olanzapine is unclear; however, its efficacy in the treatment of schizophrenia or bipolar I disorder could be mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism.

The mechanism of action of samidorphan could be mediated through opioid receptor antagonism.

Dose & Administration

ADULTS

Indication	Recommended Starting Dose (Olanzapine/Samidorphan)	Recommended Maintenance Dose (Olanzapine/Samidorphan)
Schizophrenia	5 mg/10 mg or 10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder (manic or mixed episodes)	10 mg/10 mg or 15 mg/10 mg	5 mg/10 mg 10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder adjunct to lithium or valproate	10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg

PEDIATRICS

Safety and effectiveness have not been established in pediatric patients.

GERIATRICS

A lower dosage of the olanzapine component of Lybalvi™ in geriatric patients who may have decreased clearance or an exaggerated pharmacodynamic response to olanzapine.

RENAL IMPAIRMENT

No dose adjustment of Lybalvi™ is needed in patients with mild (eGFR 60 to 89 mL/minute/1.73 m^2), moderate (eGFR 30 to 59 mL/minute/1.73 m^2), or renal impairment (eGFR 15 to 29 mL/minute/1.73 m^2).

Lybalvi™ is not recommended for patients with end-stage renal disease (eGFR of <15 mL/minute/1.73 m^2).

HEPATIC IMPAIRMENT

No dosage adjustment needed.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets (olanzapine/samidorphan): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg.