Drug Monograph

Drug Name:	**Lybalvi® (olanzapine/samidorphan) tablet**
Drug Class:	**Central Nervous System: Antipsychotics, Atypical 2nd Generation**
Prepared For:	MO HealthNet
Prepared By:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Lybalvi is available in 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg tablets.
Manufacturer:	Distributed by: Alkermes, Inc., Waltham, MA 02451.
Summary of Findings:	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 purpose of ENLIGHTEN-2 was to compare the metabolic effects of Lybalvi versus olanzapine alone. The ENLIGHTEN clinical trial program specifically assessed Lybalvi in the schizophrenia population. Efficacy of Lybalvi for the bipolar I indication was based on previously reported literature for olanzapine monotherapy. 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 in both the Lybalvi and olanzapine group experienced a statistically significant improvement in PANSS total score at Week 4 versus placebo (Difference of -6.4 and -5.3, respectively). The results demonstrated that the addition of samidorphan did not alter the antipsychotic efficacy of olanzapine. In ENLIGHTEN-2, patients were 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. Treatment with Lybalvi was associated with statistically significantly less weight gain than treatment with olanzapine (Difference of -2.4%, 95% CI: -3.9, -0.9), and a smaller proportion of patients who gained ≥10% body weight (Difference of 13.7%, 95% CI: -22.8, -4.6).

Status	☐ Clinical Edit	☐ PA Required
Recommendation:	☐ Open Access	☒ Reference List
Type of PA	☐ Appropriate Indications	☐ Reference Product
Criteria:	☐ No PA Required	☒ Non-reference Product

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Schizophrenia is a chronic psychiatric disorder that involves disturbances in cognition, emotional responsiveness, and behavior. The prevalence of schizophrenia and related psychotic disorders falls in the range between 0.25% and 0.64%. The average age of onset of schizophrenia is in the late teenage years through the early 30's. Manifestations of the disorder include: positive symptoms including delusions, hallucinations, and disorganized speech; and negative symptoms such as diminished emotional expression and avolition. In order to be diagnosed, the patient must have impaired functioning in areas such as work, self-care, or interpersonal relationships. Treatment is usually multifactorial but as far as medication, the 2nd generation antipsychotics (SGAs) are preferred over 1st generation antipsychotics due to a lower incidence of extrapyramidal side effects.

Bipolar disorder is a group of brain disorders that causes extreme fluctuations in a person's mood, energy, and ability to function. It includes three different conditions – bipolar I, bipolar II, and cyclothymic disorder.

- Bipolar I disorder is a manic-depressive disorder that can exist both with and without psychotic episodes
- Bipolar II disorder consists of depressive and manic episodes which alternate and are typically less severe and do not inhibit function
- Cyclothymic disorder is a cyclic disorder that causes brief episodes of hypomania and depression

In the United States, the prevalence of bipolar I and II disorders is estimated to fall in the range between 3.7% and 3.9%. According to the American Psychiatric Association guidelines, first-line treatment for severe manic or mixed episodes of bipolar disorder is a mood stabilizer (e.g., lithium, valproate) plus an atypical antipsychotic. For less ill patients, treatment with either a mood stabilizer or an atypical antipsychotic may be adequate. Valproate may be preferred over lithium in mixed episodes. Atypical antipsychotic agents are preferred over typical antipsychotics due to the latter's side effect profile.

Dosage Form [3]

Lybalvi is available in 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg tablets.

Manufacturer [3]

Distributed by: Alkermes, Inc., Waltham, MA 02451.

Indication(s) [3]

Lybalvi is indicated for the treatment of:

- Schizophrenia in adults
- Bipolar I disorder in adults

- Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
- Maintenance monotherapy treatment.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

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 ($5HT_2$) antagonism. The mechanism of action of samidorphan could be mediated through opioid receptor antagonism.

Pharmacokinetics:

	Olanzapine	Samidorphan
Absorption (t_{max})	4.5-7 hours	1-2 hours
Metabolism	UGT1A4, CYP1A2	CYP3A4
Excretion	Renal (64%); Fecal (30%)	Renal (85%); Fecal (16%)
Half-life	35-52 hours	7-11 hours

Clinical Trials Experience

STUDY 1 DESIGN (ENLIGHTEN; NCT02634346)	Randomized, double-blind, placebo- and active-controlled Phase 3 trial
INCLUSION CRITERIA	• Has a body mass index (BMI) of 18.0-40.0 kg/m^2 • Meets criteria for the diagnosis of schizophrenia • Resides in a stable living situation when not hospitalized
EXCLUSION CRITERIA	• Has had a psychiatric hospitalization for more than 30 days during the 90 days before screening • Subject initiated first antipsychotic treatment within the past 12 months, or <1 year has elapsed since the initial onset of active-phase of schizophrenia symptoms • Subject poses a current suicide risk • Subject has a history of treatment resistance • Subject has a history of poor or inadequate response to treatment with olanzapine • Subject requires or has had electroconvulsive therapy (ECT) treatment in the 2-month period prior to screening • Subject has a diagnosis of moderate or severe alcohol or drug use disorder • Subject has a positive urine drug screen for opioids, amphetamine/methamphetamine, phencyclidine, or cocaine at screening
TREATMENT REGIMEN	Patients were randomized 1:1:1 to receive Lybalvi, olanzapine, or placebo. Patients could receive up to 20 mg of olanzapine in both study arms.
RESULTS	The primary efficacy endpoint was the change from baseline PANSS* total score at Week 4.

	Total PANSS Score	
Treatment Group	**LS mean Change from Baseline**	**Placebo-Subtracted Difference (95% CI)**
Lybalvi (N=132)	-23.9	-6.4 (-10.0, -2.8)

<table>
<tr><td></td><td>
<table>
<tr><td>Placebo (N=133)</td><td>-17.5</td><td>-</td></tr>
<tr><td>Olanzapine (N=132)</td><td>-22.8</td><td>-5.3 (-8.9, -1.7)</td></tr>
</table>
Abbreviations: LS=least squares; PANSS= Positive and Negative Syndrome Scale; CI=confidence interval

Patients in both the Lybalvi and olanzapine group experienced a statistically significant improvement in PANSS total score at Week 4 versus placebo. The addition of samidorphan did not alter antipsychotic efficacy of olanzapine.</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
</table>

* The PANSS scale measures the various symptoms of schizophrenia, with a higher score equating to greater symptom severity

<table>
<tr><td>STUDY 2 DESIGN (ENLIGHTEN-2; NCT02694328)</td><td>Randomized, 24-week Phase 3 trial</td></tr>
<tr><td>INCLUSION CRITERIA</td><td>• Age 18-55 years
• Meets DSM-5 criteria for a primary diagnosis of schizophrenia
• Naïve to antipsychotic medication
• BMI between 18 and 30 kg/m^2
• Stable body weight (self-reported change ≤5%) for at least 3 months before study initiation</td></tr>
<tr><td>EXCLUSION CRITERIA</td><td>• 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</td></tr>
<tr><td>TREATMENT REGIMEN</td><td>Patients were 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.</td></tr>
<tr><td>RESULTS</td><td>Co-primary endpoints were: the percent change from baseline in body weight, and the proportion of patients who gained ≥10% of body weight at Week 24. A key secondary endpoint was the proportion of patients with ≥7% weight gain at Week 24.

<table>
<tr><th rowspan="2">Treat-ment Group</th><th colspan="3">% Change from baseline in Body Weight</th><th colspan="2">≥10% Body Weight Gain</th><th colspan="2">≥7% Body Weight Gain</th></tr>
<tr><th>Baseline Mean, kg</th><th>LS Mean % Change from baseline</th><th>Difference vs. OLZ (95% CI)</th><th>% of Pa-tients</th><th>Difference vs. OLZ (95% CI)</th><th>% of Pa-tients</th><th>Difference vs. OLZ (95% CI)</th></tr>
<tr><td>Lybalvi (N=266)</td><td>77.0</td><td>4.2</td><td rowspan="2">-2.4 (-3.9, -0.9)</td><td>17.8%</td><td rowspan="2">-13.7% (-22.8, -4.6)</td><td>27.5%</td><td rowspan="2">-15.2%</td></tr>
<tr><td>OLZ (N=272)</td><td>77.5</td><td>6.6</td><td>29.8%</td><td>42.7%</td></tr>
</table>
Abbreviations: OLZ=olanzapine

Treatment with Lybalvi was associated with statistically significantly less weight gain than treatment with olanzapine, and with a smaller proportion of patients who gained ≥10% body weight.</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
</table>

Contraindications [3,4]

- 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.

Warnings and Precautions [3,4]

- 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: 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.

Adverse Effects [3,4]

Most common, ≥2%	Lybalvi (10 mg/10 mg, 20 mg/10 mg) (N=134) %	Placebo (N=134) %
Weight increased	19	3
Somnolence	9	2
Dry mouth	7	1
Headache	6	3
Blood insulin increased	3	1
Sedation	2	0
Dizziness	2	1
Neutrophil count decreased	2	0

Drug Interactions [3,4]

- Strong CYP3A4 Inducers: Not recommended.
- Strong CYP1A2 Inhibitors: Consider dosage reduction of olanzapine component of Lybalvi.
- CYP1A2 Inducer: Consider dosage increase of the olanzapine component of Lybalvi.
- CNS Acting Drugs: May potentiate orthostatic hypotension.
- Anticholinergic Drugs: Can increase risk for severe gastrointestinal adverse reactions.
- Antihypertensive Agents: Monitor blood pressure.
- Levodopa and Dopamine Agonists: Not recommended.

Dosage and Administration [3,4]

- Administer once daily with or without food.
- Schizophrenia:
  - Starting Dose: 5 mg/10 mg or 10 mg/10 mg once daily
  - Recommended Dose: 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily
  - Dose may be adjusted by 5 mg of olanzapine at weekly intervals up to the maximum dose of 20 mg/10 mg once daily
- Bipolar I disorder (manic or mixed episodes):
  - Acute Treatment Monotherapy:
    - Starting Dose: 10 mg/10 mg or 15 mg/10 mg once daily
    - Recommended Dose: 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily
    - Dose may be adjusted by 5 mg of olanzapine at intervals of at least 24 hours up to the maximum dose of 20 mg/10 mg once daily
  - Maintenance Monotherapy:
    - 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily
  - Adjunct to lithium or valproate:
    - Starting Dose: 10 mg/10 mg once daily
    - Recommended Dose: 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily
    - Dose may be adjusted by 5 mg of olanzapine at weekly intervals up to the maximum dose of 20 mg/10 mg once daily
- For patients that have a higher risk of hypotensive reactions, are at risk of slower olanzapine metabolism, or may be more pharmacodynamically sensitive to olanzapine,

the recommended starting dosage of Lybalvi is 5 mg/10 mg once daily. If dose escalation is needed, increase the dosage slowly.

- In patients who use opioids, delay initiation of Lybalvi for a minimum of 7 days after last use of short-acting opioids and 14 days after last use of long-acting opioids.
- When considering a switch to Lybalvi from olanzapine, the change should be made within the first year of therapy. Long term studies have shown that weight gain stabilizes after 1 year on olanzapine therapy.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Olanzapine/Samidorphan	Lybalvi®	Alkermes	10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily	$1,390
Lurasidone	Latuda®	Sunovion	80 mg once daily	$1,365
Brexpiprazole	Rexulti®	Otsuka America	3 mg once daily	$1,264
Iloperidone	Fanapt®	Vanda	8 mg twice daily	$1,274
Cariprazine	Vraylar®	Allergan	4.5 mg once daily	$1,294
Lumateperone	Caplyta®	Intra-Cellular Therapies	42 mg once daily	$1,419
Olanzapine	Zyprexa®	Eli Lilly	15 mg once daily	$4.83

** Wholesale Acquisition Cost

Conclusion

Lybalvi is indicated for the treatment of schizophrenia in adults and for the treatment of bipolar I disorder in adults as: a maintenance monotherapy; or for the acute treatment of manic or mixed episodes and as an adjunct to lithium or valproate. Lybalvi is a single-tablet combination treatment designed to provide the efficacy of olanzapine while mitigating olanzapine-associated weight gain through the addition of samidorphan, an opioid antagonist. The ENLIGHTEN-1 trial established similar efficacy between Lybalvi and olanzapine versus placebo. ENLIGHTEN-2 showed less weight gain with Lybalvi than with olanzapine monotherapy, with a 2.4% difference in change from baseline in body weight. No new safety concerns were found with the addition of samidorphan to olanzapine. However, Lybalvi is contraindicated in patients using opioids and in patients undergoing opioid withdrawal because samidorphan is an opioid antagonist.

Recommendation

This drug is being considered for inclusion in the state specific Antipsycholtics, 2nd Generation Reference List as a non-reference product.

References

1) National Alliance on Mental Illness. Schizophrenia. Available at: https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Schizophrenia. Accessed June 2021.
2) National Alliance on Mental Illness. Bipolar Disorder. Available at: https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Bipolar-Disorder. 2020. Accessed June 2021.
3) Lybalvi™ (olanzapine and samidorphan) [package insert]. Waltham, MS: Alkermes; 2021.
4) IPD Analytics. Rx Insights New Drug Review Lybalvi. July 2021.

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