PDL DRUG REVIEW

Proprietary Name: Lybalvi®
Common Name: olanzapine and samidorphan L-malate
PDL Category: Antipsychotics

Comparable Products	Preferred Drug List Status
Aripiprazole	Preferred
Olanzapine	Preferred
Quetiapine	Preferred
Risperidone	Preferred

Summary

Pharmacology/Usage: Lybalvi® is a combination of olanzapine (an atypical antipsychotic) and samidorphan (as samidorphan L-malate; an opioid antagonist). The mechanism of action of olanzapine is not clear; however its efficacy in the treatment for its approved indications could be mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of samidorphan may be mediated through opioid receptor antagonism.

Indication: 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

There is no pregnancy category for this medication; however, the risk summary indicates that neonates exposed to antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Overall published epidemiologic studies of pregnant women exposed to olanzapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are no available data on the use of samidorphan or the combination of olanzapine and samidorphan in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics during pregnancy. Healthcare providers are encouraged to register patients by calling 1-866-961-2388 or online at https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Tablets containing olanzapine/samidorphan: 5mg/10mg, 10mg/10mg, 15mg/10mg, 20mg/10mg. Do not divide tablets or combine strengths.

Recommended Dosage: Use is contraindicated in patients using opioids or undergoing acute opioid withdrawal. 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.

For schizophrenia, start Lybalvi® at 5mg/10mg or 10mg/10mg PO QD. The recommended dosage is 10mg/10mg, 15mg/10mg, or 20mg/10mg QD.

For bipolar I disorder, start Lybalvi® for monotherapy at 10mg/10mg or 15mg/10mg QD. The recommended dosage is 10mg/10mg or 15mg/10mg, or 20mg/10mg QD. Dosage adjustments should occur at intervals of not less than 24 hours. *For maintenance monotherapy*, administer Lybalvi® at 5mg/10mg, 10mg/10mg, 15mg/10mg, or 20mg/10mg QD. *For bipolar I disorder as adjunctive to lithium or valproate*, initiate Lybalvi® at 10mg/10mg QD. The recommended dosage is 10mg/10mg, 15/10mg, or 20mg/10mg QD.

For either indication, dosage may be adjusted at weekly intervals of 5mg (based on the olanzapine component) depending upon clinical response and tolerability, up to the maximum recommended dosage of 20mg/10mg QD. Administer Lybalvi® with or without food as a single tablet.

The recommended starting dosage of Lybalvi® is 5mg/10mg QD in patients who have a higher risk of hypotensive reactions, are at risk of slower olanzapine metabolism, or may be more pharmacodynamically sensitive to olanzapine. If dose escalation is necessary, increase the dosage slowly in these patients.

Dose adjustment is not required with hepatic or renal impairment. Lybalvi® is not recommended for patients with end-stage renal disease.

Drug Interactions: Concomitant use of Lybalvi® with strong CYP3A4 inducers is not recommended.

Consider reducing the dosage of the olanzapine component in Lybalvi® when used concomitantly with strong CYP1A2 inhibitors.

Consider increasing the dosage of the olanzapine component in Lybalvi® when used concomitantly with CYP1A2 inducers.

Lybalvi® should be used with caution in patients receiving concomitant diazepam or other CNS acting drugs or using alcohol.

Lybalvi® should be used with caution in patients receiving medications having anticholinergic (antimuscarinic) effects.

Lybalvi® may enhance the effects of certain antihypertensive agents; thus, monitor blood pressure and reduce the dosage of the antihypertensive drug per its approved product labeling.

Concomitant use of Lybalvi® is not recommended with levodopa and dopamine agonists.

Opioids: Lybalvi® is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Lybalvi® increases the risk of precipitating acute 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.

In emergency situations, if a Lybalvi®-treated patient requires opioid treatment for anesthesia or analgesia, discontinue Lybalvi®. The opioid should be administered by properly trained individuals and the patient should be properly monitored in a setting equipped and staffed for cardiopulmonary resuscitation.

In non-emergency situations, if a Lybalvi®-treated patient is expected to require opioid treatment (e.g. for analgesia during or after an elective surgical procedure) discontinue Lybalvi® at least 5 days before opioid treatment and start olanzapine or another antipsychotic, if needed.

Given that Lybalvi® contains samidorphan, an opioid antagonist, opioid treatment may be less effective or ineffective shortly after Lybalvi® discontinuation because of the presence of samidorphan.

Box Warning: Lybalvi® has a box warning regarding increased mortality in elderly patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Lybalvi® is not approved for the treatment of patients with dementia-related psychosis.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Lybalvi®) minus reported % incidence for placebo in a 4-week schizophrenia trial. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included weight increased (16%), somnolence (7%), dry mouth (6%), headache (3%), blood insulin increased (2%), sedation (2%), dizziness (1%), and neutrophil count decreased (2%).

Cerebrovascular adverse reactions, including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. Lybalvi® is not approved for the treatment of patients with dementia-related psychosis.

Samidorphan, an opioid antagonist, can precipitate opioid withdrawal in patients who are dependent on opioids, which can lead to an opioid withdrawal syndrome, sometimes requiring hospitalization. Thus, Lybalvi® is contraindicated in patients who are using opioids or are undergoing acute opioid withdrawal. Prior to starting Lybalvi®, there should be at least a 7-day opioid free interval from last use of short-acting opioids, and at least a 14-day opioid free interval from the last use of long-acting opioids.

Attempting to overcome Lybalvi® opioid blockade with high or repeated doses of exogenous opioids could lead to life-threatening or fatal opioid intoxication (e.g. respiratory arrest, circulatory collapse), especially if Lybalvi® therapy is interrupted or discontinued, subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes. Inform patients of the potential consequences of trying to overcome the opioid blockade and the serious risks of taking opioids concurrently with Lybalvi® or while transitioning off Lybalvi®. In emergency situations, if a Lybalvi®-treated patient requires opioid treatment as part of anesthesia or analgesia:

- Discontinue Lybalvi®
- Opioids should be administered by individual(s) trained in the use of anesthetic drugs and the management of the respiratory effects of opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation, and
- Appropriately trained personnel should continuously monitor the patient in a setting equipped and staffed for cardiopulmonary resuscitation.

Patients with a history of chronic opioid use prior to treatment with Lybalvi® may have decreased opioid tolerance if Lybalvi® therapy is interrupted or discontinued. Advise patients that this decreased tolerance may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage.

Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. If NMS is suspected, discontinue Lybalvi® immediately and provide symptomatic treatment and monitoring.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with exposure to olanzapine. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications. Discontinue Lybalvi® if DRESS is suspected.

Atypical antipsychotics, including Lybalvi®, have been associated with metabolic changes that include hyperglycemia, diabetes mellitus, dyslipidemia, and body weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. Patients starting treatment with Lybalvi® should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment, as well as undergo fasting lipid profile testing at the beginning of treatment and periodically during treatment. Monitor weight for weight gain prior to starting Lybalvi® and frequently thereafter.

Tardive dyskinesia may develop in patients treated with antipsychotic drugs. Although the risk appears to be highest among the elderly, especially elderly women, it is not possible to predict who will develop the syndrome. The risk of developing tardive dyskinesia and the chance that it will become irreversible increases with the duration of treatment and the cumulative dose. Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Lybalvi® should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient treated with Lybalvi®, drug discontinuation should be considered. However, some may require treatment with Lybalvi® despite the presence of the syndrome.

Atypical antipsychotics can cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. Monitor orthostatic vital signs in patients who are vulnerable to hypotension, patients with known cardiovascular disease, and patients with cerebrovascular disease. Lybalvi® has not been evaluated in patients with a recent history of MI or unstable cardiovascular disease. Such patients were excluded from the premarketing clinical trials.

Antipsychotics, including Lybalvi®, may cause somnolence, postural hypotension, as well as motor and sensory instability, which may lead to falls, and consequently fractures or other injuries.

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including Lybalvi®. Agranulocytosis has been reported with other agents in the class. In patients with a pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) or a history of drug-induced leukopenia or neutropenia, perform a complete blood count frequently during the first few months of therapy. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat if symptoms or signs occur. Discontinue Lybalvi® in patients with severe neutropenia (ANC <1000/mm^3) and follow the WBC until recovery.

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including Lybalvi®, should be used cautiously in patients at risk for aspiration.

Like other antipsychotic drugs, Lybalvi® may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

Lybalvi®, like other antipsychotics, may cause somnolence and has the potential to impair judgement, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that Lybalvi® therapy does not adversely affect them.

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use Lybalvi® with caution in patients who experience these conditions.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with oral olanzapine, it was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuation, but Lybalvi® should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, constipation, or a history of paralytic ileus or related conditions.

Like other drugs that antagonize dopamine D2 receptors, olanzapine elevates prolactin levels and the elevation can persist during chronic administration.

Contraindications: In patients:

- Who are using opioids
- Who are undergoing acute opioid withdrawal

If Lybalvi® is administered with lithium or valproate, refer to the lithium or valproate prescribing information for the contraindications for these products.

Manufacturer: Alkermes, Inc.

Analysis: The safety and efficacy of Lybalvi® *for the treatment of schizophrenia* in adults is based, in part, upon adequate and well-controlled studies of orally administered olanzapine. The efficacy of Lybalvi® was also assessed in a 4-week, randomized, double-blind, placebo- and active-controlled study (study 1). In this study, adults met DSM-5 criteria for schizophrenia and were randomized to Lybalvi®, olanzapine, or placebo for 4 weeks of daily dosing. The study was designed to compare Lybalvi® with placebo, not with olanzapine.

Included patients in study 1 were 18 to 70 years of age, had a body mass index (BMI) of 18-40 kg/m^2, had a Positive and Negative Syndrome Scale (PANSS) total score of ≥80, a score of ≥4 on at least 3 of the selected Positive Scale items, and were required to have a Clinical Global Impression-Severity (CGI-S) score ≥4.

The primary efficacy endpoint was the change from baseline in PANSS total score at week 4. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme). Total PANSS scores range from 30 to 210, with a higher score reflecting greater symptom severity. The secondary efficacy endpoint was defined as the change from baseline in CGI-S score at week 4, which is a validated scale that requires clinicians to rate a patient's current illness severity and overall clinical state based on experience with the illness population. The scores range from 1 (normal, not at all ill) to 7 (extremely ill).

Results suggested that compared with placebo, a statistically significant improvement in the change from baseline in PANSS total score at week 4 was observed in patients treated with Lybalvi®. The inclusion of samidorphan in Lybalvi® did not appear to negatively impact the antipsychotic efficacy of olanzapine. Results can be observed in the table below, which was adapted from the prescribing information.

Treatment group	Total PANSS Score		
	Baseline Mean Score	LS Mean change from baseline	Placebo-subtracted difference *
Lybalvi® 10mg/10mg, 20mg,10mg (N=132)	101.8	-23.9	-6.4
Placebo (N=133)	102.7	-17.5	
Olanzapine 10mg, 20mg (N=132)	100.6	-22.8	-5.3

*Difference (drug minus placebo) in least squares mean change from baseline. A negative value for the placebo subtracted difference represents improvement.

Compared with the patients on placebo, a statistically significant improvement in CGI-S score at week 4 was observed in patients treated with Lybalvi®.

In study 2, adult patients who met DSM-5 criteria for schizophrenia were randomized to Lybalvi® or olanzapine for 24 weeks of daily dosing, treated with doses of Lybalvi® 10mg/10mg or 20mg/10mg or with doses of olanzapine 10mg or 20mg. Eligible patients were 18 to 55 years of age with a BMI of 18 to 30 kg/m^2, had a PANSS total score of 50 to 90, a CGI-S score of ≤4, and symptoms suitable for outpatient treatment. Patients with diabetes were excluded. Furthermore, the proportion of patients who discontinued study drug in the 24-week trial was 36% for both the Lybalvi® and olanzapine-treated groups.

The co-primary endpoints were percent change from baseline in body weight and the proportion of patients who gained ≥10% body weight at week 24. Lybalvi® was compared to olanzapine. Patients on stable, chronic olanzapine therapy were not specifically studied, so the weight effect of switching from olanzapine to Lybalvi® is unknown. Results suggested that 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. Results can be seen in the table below, which was adapted from the prescribing information.

Treatment group	% Change from Baseline in Body Weight		
	Baseline Mean, kg	LS Mean % change from baseline	olanzapine-subtracted difference
Lybalvi® 10mg/10mg, 20mg,10mg (N=266)	77.0	4.2	-2.4
Olanzapine 10mg, 20mg (N=272)	77.5	6.6	-

Treatment Group	≥10% Body Weight Gain	
	% of patients	olanzapine-subtracted Risk Difference
Lybalvi® 10mg/10mg, 20mg,10mg (N=266)	17.8	-13.7
Olanzapine 10mg, 20mg (N=272)	29.8	-
NNT *calculated by CHC*	8	

The efficacy of Lybalvi® *for the treatment of bipolar I disorder in adult patients* has been established based on adequate and well-controlled studies of orally administered olanzapine. The information in the prescribing information describes the results of adequate and well-controlled studies of olanzapine in patients with bipolar I disorder. Olanzapine, both as brand Zyprexa® and generic, have been available for many years and found to be safe and effective for this indication.

Place in Therapy: Lybalvi® is a combination product containing olanzapine (atypical antipsychotic) and samidorphan (an opioid antagonist) that is indicated for the treatment of schizophrenia in adults and for the treatment of bipolar I disorder in adults (as acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate, as well as for maintenance monotherapy treatment). Lybalvi® is contraindicated in patients who are using opioids and in patients who are undergoing acute opioid withdrawal. In a double-blind, placebo- and active controlled study that included adults who met DSM-5 criteria for schizophrenia, adults were randomized to Lybalvi®, olanzapine, or placebo; however, the study was designed to compare Lybalvi® with placebo, not with olanzapine. Results suggested that compared with placebo, a statistically significant improvement in the change from baseline in PANSS total score at week 4 was observed in patients treated with Lybalvi®. The inclusion of samidorphan in Lybalvi® did not appear to negatively impact the antipsychotic efficacy of olanzapine. Furthermore, in a second study that compared Lybalvi® with olanzapine in patients with schizophrenia, weight gain was assessed. Treatment with Lybalvi® was associated with statistically significantly less weight gain than with olanzapine alone and with a smaller proportion of patients who gained ≥10% body weight.

While there is some evidence at this time to suggest Lybalvi® may have less weight gain as compared with olanzapine alone, there is no evidence that Lybalvi® is more effective than olanzapine. In addition, there is no evidence to support that Lybalvi® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Lybalvi® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred Step 3**

References

[1] Lybalvi [package insert].Waltham, MA: Alkermes, Inc; 2021.