Olanzapine/samidorphan (Lybalvi™) Drug Bulletin

June 2021

<table>
<thead>
<tr>
<th>Nonproprietary Name</th>
<th>olanzapine/samidorphan</th>
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<tr>
<td>Brand Name</td>
<td>Lybalvi</td>
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<tr>
<td>Manufacturer</td>
<td>Alkermes</td>
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<tr>
<td>FDA Approval Date</td>
<td>May 28, 2021</td>
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<tr>
<td>Market Availability Date</td>
<td>Anticipated 4Q 2021</td>
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**Indication**

Treatment of:
1) schizophrenia in adults
2) bipolar I disorder in adults
   a) for the acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
   b) for maintenance monotherapy treatment

**Dosage Form**

Oral tablets (olanzapine/samidorphan): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, and 20 mg/10 mg

**Dosage**

Max dose for all indications is 20 mg/10 mg once daily

Schizophrenia - initial dose 5 mg/10 mg or 10 mg/10 mg once daily; adjustments at weekly intervals of 5 mg to 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg

Bipolar I disorder (monotherapy) - initial dose 10 mg/10 mg or 15 mg/10 mg once daily; titration at intervals of no less than 24 hours in 5 mg increases/decreases to a dose of 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg; the maintenance monotherapy doses are 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg

Bipolar I disorder (adjunct to lithium or valproate) - initial dose 10 mg/10 mg once daily; adjustments at weekly intervals in 5 mg to a dose of 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg

**CLINICAL CONSIDERATIONS**

- Olanzapine/samidorphan (Lybalvi) is a combination of the atypical antipsychotic olanzapine (Zyprexa® Relprev™, Zyprexa® Zydis®, Zyprexa®, generics) and the opioid antagonist samidorphan (new molecular entity). Olanzapine’s efficacy may be mediated through dopamine and serotonin type 2 (5HT2) antagonism, and samidorphan’s activity may be mediated through antagonism of the opioid receptor. ¹

- Safety² – Due to the samidorphan component, Lybalvi may precipitate severe opioid withdrawal in patients who are physiologically dependent on opioids; therefore, use of Lybalvi is contraindicated
in patients who are using opioids and in those who are undergoing acute opioid withdrawal. Lybalvi carries a warning for vulnerability to life-threatening opioid overdose due to potential attempts at overcoming the samidorphan blockade; those with a history of chronic opioid use, before treatment, may have a reduced opioid tolerance if Lybalvi is interrupted or discontinued.

- Lybalvi carries a boxed warning for increased mortality in elderly patients with dementia-related psychosis, and it is not approved for treating patients with dementia-related psychosis. It also carries a warning for cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis (olanzapine component).³

- The following additional warnings are also attributed to the olanzapine component, some of which could lead to fatal events: neuroleptic malignant syndrome (NMS); Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); metabolic changes (e.g., hyperglycemia, diabetes mellitus, dyslipidemia, body weight gain), tardive dyskinesia (potentially irreversible); orthostatic hypotension and syncope; falls, fractures, or other injuries; leukopenia, neutropenia, and agranulocytosis; dysphagia leading to esophageal dysmotility and aspiration; seizures (greatest risk in those with past history or who have conditions lowering seizure threshold); potential for cognitive and motor impairment due to somnolence (caution with operating hazardous machinery); body temperature dysregulation; anticholinergic effects; hyperprolactinemia leading to inhibited reproductive function (resulting in galactorrhea, amenorrhea, gynecomastia, impotence, decreased bone density).

- The most common adverse effects (AEs) during the 4-week trial, occurring in ≥ 5% and at least twice the rate of placebo in patients with schizophrenia who received Lybalvi compared to placebo, respectively, were weight increased (19% versus 3%), somnolence (9% versus 2%), dry mouth (7% versus 1%), and headache (6% versus 3%). In the 24-week trial of stable schizophrenia, the most common AEs occurring in ≥ 5% of patients treated with Lybalvi included weight increased (25%), somnolence (21%), dry mouth (13%), increased appetite (11%), waist circumference increased (6%), and blood creatine phosphokinase (CPK) increased (5%).⁴

- Drug interactions⁵ –
  - Strong cytochrome P450 (CYP) 3A4 inducer: Concurrent use is not recommended as the inducer can decrease exposure to olanzapine and samidorphan, thereby decreasing efficacy
  - Strong CYP1A2 inhibitor: Consider decreasing the dose of the olanzapine component when used, as concurrent use increases olanzapine exposure, which may increase the risk for AEs
  - CYP1A2 inducer: Consider increasing the dose of the olanzapine component when used, as concurrent use decreases olanzapine exposure, which may decrease Lybalvi efficacy
  - Diazepam, alcohol, and other central nervous system (CNS) acting drugs: Use with caution in patients concurrently using these medications as the hypotensive effects of olanzapine may be potentiated
  - Anticholinergics: Use with caution in patients taking anticholinergic medications as concurrent use can increase the risk of severe gastrointestinal (GI) AEs (hypomotility)
- **Antihypertensives**: Monitor blood pressure (BP) and reduce the dose of antihypertensives, if needed, as Lybalvi may increase the impact of certain antihypertensives.

- **Levodopa and dopamine agonists**: As Lybalvi may antagonize the effects, concurrent use is not recommended.

- **Opioids**: In patients who use opioids, starting Lybalvi should be delayed for ≥ 7 days following discontinuation of short-acting opioids and 14 days after discontinuation of long-acting opioids; if an elective surgery is planned and use of opioids is expected, Lybalvi should be discontinued ≥ 5 days prior to opioid therapy and initiate olanzapine or another agent; opioid therapy may be less effective/ineffective shortly following Lybalvi discontinuation.

- **Special populations – pregnancy**: no data are available on use of samidorphan or Lybalvi in pregnant women to determine a drug-associated risk for adverse outcomes; however, neonates exposed to antipsychotics (olanzapine) during the 3rd trimester are at increased risk for extrapyramidal and/or withdrawal symptoms after delivery; **females of reproductive potential**: olanzapine may lead to an increase in prolactin levels leading to a reversible decrease in fertility; **renal impairment**: not recommended to be used in end-stage renal disease (ESRD) as it has not been studied.

- **Lybalvi** was approved via the 505(b)(2) pathway, hence at least a portion of the data supporting its approval may have been derived from another formulation/another manufacturer; efficacy in adults with **bipolar I disorder** was previously established based on adequate and well-controlled studies of orally administered olanzapine. Efficacy in **schizophrenia** was based on previously conducted studies evaluating oral olanzapine in adults and a 4-week, randomized, double-blind, placebo- and active-controlled study (NCT02634346; ENLIGHTEN-1) conducted in adults who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for schizophrenia and were experiencing an **acute exacerbation**. Dosing was dependent on response and tolerability for the first 2 weeks of the study and then fixed thereafter: Lybalvi (n=132; 10 mg/10 mg or 20 mg/10 mg), olanzapine (n=132; 10 mg or 20 mg), or placebo (n=133). Patients were required to have a Positive and Negative Syndrome Scale (PANSS) total score of ≥ 80 (higher score reflecting greater symptom severity) and Clinical Global Impression-Severiy (CGI-S) score ≥ 4. At week 4, a statistically significant improvement in the change from baseline in PANSS total score was seen in Lybalvi-treated patients compared to placebo with a least squares mean (LSM) change in the placebo-subtracted difference of -6.4 (95% confidence interval [CI], -10 to -2.8); in comparison in the olanzapine arm, the placebo-subtracted difference was -5.3 (95% CI, -8.9 to -1.7). At week 4, a statistically significant improvement in the secondary endpoint, CGI-S score, was also seen in Lybalvi-treated patients compared to placebo.

- A separate phase 3, double-blind, 24-week study (NCT02694328; ENLIGHTEN-2) was conducted to evaluate the effect on weight in adults who met DSM-5 criteria for schizophrenia. Patients with PANSS total score of 50 to 90, CGI-S score of ≤ 4, and symptoms suitable for outpatient treatment were randomized 1:1 to receive either Lybalvi (n=280; 10 mg/10 mg or 20 mg/10 mg) or olanzapine (n=281; 10 mg or 20 mg). The coprimary endpoints were percentage change from...
baseline in body weight and the proportion of patients who gained ≥ 10% body weight by week 24. Lybalvi resulted in significantly less weight gain than olanzapine (LSM percentage weight change from baseline 4.21% versus 6.59%, respectively; olanzapine-subtracted difference -2.38%; 95% CI, -3.9 to -0.9). In addition, significantly less patients in the Lybalvi group compared with the olanzapine group had ≥ 10% weight gain (17.8% versus 29.8%; difference -13.7%; 95% CI, -22.8 to -4.6; odds ratio 0.5; number-needed-to-treat 7.29). Improvement in schizophrenia symptoms were similar between study arms, and patients in the Lybalvi group demonstrated smaller increases in waist circumferences compared with olanzapine-treated patients; metabolic changes were small and comparable between study arms.

- **Schizophrenia** – Although the guidelines do not currently address Lybalvi or samidorphan due to the date of publication, the olanzapine component of Lybalvi is addressed. The American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Schizophrenia, 3rd edition – 2020, includes olanzapine as a second-generation antipsychotic and describes the impact of weight gain with olanzapine and the risk for metabolic syndrome.  

- **Bipolar disorder** - The International College of Neuropsychopharmacology (CINP) provided a proposed algorithm for adults with bipolar disorder in their 2017 guidelines and assessment of other international guidelines and published literature. Olanzapine is recommended as a monotherapy, first-line treatment option for depressive predominant polarity or no dominant polarity; olanzapine monotherapy is also a potential first-line option for manic predominant polarity. In patients with mixed episodes, they recommend a mood stabilizer with olanzapine or aripiprazole. The World Federation of Societies of Biological Psychiatry (WFSBP) has also provided a series of guidance on the treatment of bipolar disorder (2009, 2010, 2013, and 2017). Olanzapine is included as an antipsychotic treatment option for acute mania (A, 2), acute bipolar I depression (B, 3), and for long-term maintenance as an overall recommendation based on evidence across episodes (recommendation grade 2).

- Olanzapine/samidorphan (Lybalvi) is marketed as providing the antipsychotic efficacy seen with olanzapine with less weight gain. The FDA’s review concluded that Lybalvi had expected atypical antipsychotic class effects with no new safety concerns and demonstrated the potential for mitigation of weight gain; however, as Lybalvi contains samidorphan, an opioid antagonist, there is the potential for safety concerns regarding concurrent opioid use. Oral olanzapine (Zyprexa, generics) shares the FDA-approved indications of Lybalvi for the treatment of schizophrenia and bipolar I disorder in adults and is also indicated for adolescents (ages 13 to 17 years old) with these conditions.
## SUGGESTED UTILIZATION MANAGEMENT

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<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
<th>Initial Approval Criteria</th>
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<td>Clinical Edit</td>
<td>Antipsychotics</td>
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### Initial Approval Criteria
- Patient is ≥ 18 years; AND
- Patient has a diagnosis of schizophrenia OR bipolar I disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); AND
- If used for bipolar I disorder, will be used for either:
  - acute treatment of manic or mixed episodes as monotherapy OR as adjunct to lithium or valproate; OR
  - maintenance monotherapy treatment; AND
- Patient is NOT currently using opioids; AND
- Patient is NOT undergoing acute opioid withdrawal; AND
- If the patient has a history of chronic opioid use, patient will be counseled on the potential for decreased opioid tolerance if Lybalvi therapy is interrupted/discontinued which may increase the risk of opioid overdose if opioids are resumed at the previously tolerated dosage; AND
- Patient will be monitored for development of signs/symptoms related to neuroleptic malignant syndrome (NMS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), body temperature dysregulation, severe cognitive or motor impairment, seizures, dysphagia, severe anticholinergic effects, and hyperprolactinemia; AND
- Patient will receive fasting blood glucose testing at the initiation of therapy with Lybalvi and periodically during treatment to monitor for hyperglycemia; AND
- Patient will receive fasting lipid profile testing at the initiation of therapy with Lybalvi and periodically during treatment to monitor for dyslipidemia; AND
- Patient will have body weight monitored before starting Lybalvi and frequently thereafter; AND
- Patient will be periodically reassessed for the need for continued therapy due to the potential for tardive dyskinesia; AND
- If the patient is vulnerable to hypotension (e.g., elderly, dehydration, hypovolemia, known cardiovascular disease [CVD]) or has cerebrovascular disease, orthostatic vital signs will be monitored periodically; AND
- Patient has NOT recently had an myocardial infarction (MI) or unstable cardiovascular disease; AND
- If patient has an underlying condition or concurrent medication that could exacerbate the likelihood for falls, a fall risk assessments should be conducted when starting Lybalvi and recurrently if used for an extended period of time; AND
- If patient has pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) or a history of drug-induced
leukopenia or neutropenia, a complete blood count (CBC) will be performed frequently during the first few months of therapy; AND

- Patient will NOT be on concomitant therapy with any of the following:
  - Strong cytochrome P450 (CYP) 3A4 inducer; AND
  - Levodopa and dopamine agonists

- Patient does NOT have end-stage renal disease (ESRD); AND
- Patient has a body mass index (BMI) of ≥ 18 kg/m²; AND
- Patient has had a trial and failure of ≥ 1 second-generation (atypical) antipsychotic (e.g., risperidone); AND
- Prescriber attestation weight gain and/or metabolic changes necessitate the use of Lybalvi.

Renewal Criteria

- Patient must continue to meet the above criteria; AND
- Patient must have disease improvement and/or stabilization; AND
- Patient has NOT experienced any treatment-restricting adverse effects (e.g., NMS, DRESS, severe metabolic changes; tardive dyskinesia, orthostatic hypotension, syncope, falls, neutropenia, leukopenia, agranulocytosis, dysphagia, seizures, severe cognitive or motor impairment, severe body temperature dysregulation, severe anticholinergic adverse effects, severe hyperprolactinemia).

Quantity Limit

Max dose for all indications is 20 mg/10 mg once daily
30 tablets/30 days for all strengths (5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, and 20 mg/10 mg)

Duration of Approval

Initial: 6 months
Renewal: 12 months

Drug to Disease Hard Edit

Dementia-related psychosis; acute opioid withdrawal

REFERENCES

1 Lybalvi [package insert]. Waltham, MA; Alkermes; May 2021.
2 Lybalvi [package insert]. Waltham, MA; Alkermes; May 2021.
3 Lybalvi [package insert]. Waltham, MA; Alkermes; May 2021.
4 Lybalvi [package insert]. Waltham, MA; Alkermes; May 2021.
5 Lybalvi [package insert]. Waltham, MA; Alkermes; May 2021.
6 Lybalvi [package insert]. Waltham, MA; Alkermes; May 2021.
7 FDA approval letter. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/213378Orig1s000,%20Orig2s000ltr.pdf. Accessed June 27, 2021.
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9 Lybalvi [package insert]. Waltham, MA; Alkermes; May 2021.
11 Lybalvi [package insert]. Waltham, MA; Alkermes; May 2021.


20 Center for Drug Evaluation and Research. Application number: 213378Orig1s000, 213378Orig2s000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213378Orig1Orig2s000MultidisciplineR.pdf. Accessed June 28, 2021.

21 Zyprexa [package insert]. Indianapolis, IN; Eli Lilly; October 2019.