

Olanzapine-samidorphan combination for schizophrenia or bipolar I disorder

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Approved by the FDA on May 28, 2021, olanzapine-samidorphan combination (OSC) (Lybalvi, manufactured and distributed by Alkermes, Inc. Waltham, MA USA) is intended to help mitigate some of the weight gain that can be anticipated with the use of olanzapine alone (*Table, page 36*).¹⁻³ Olanzapine (Zyprexa, originally manufactured and distributed by Eli Lilly and Company/Lilly USA, LLC, Indianapolis, IN USA) is a second-generation antipsychotic that has been available for a quarter century.⁴ Although highly efficacious,^{5,6} olanzapine has been associated with weight gain, at times substantial, as well as disturbances in glucose and lipid metabolism.⁷ The addition of samidorphan, an opioid antagonist, to olanzapine in a single tablet may act to decrease the amount of long-term weight gain that can be expected for some patients taking olanzapine alone, consequently minimizing the anticipated increase in waist circumference (a proxy for the measurement of burden imposed by metabolically active adipose tissue). Approval of OSC for the treatment of schizophrenia was based on 2 pivotal randomized controlled trials and their extension studies.⁸⁻¹¹ Approval of OSC for bipolar I disorder (acute treatment of manic/mixed episodes as a monotherapy or adjunctive to lithium or valproate, and as a monotherapy maintenance treatment) was based on legacy studies conducted with olanzapine, after establishing that samidorphan does not alter the pharmacokinetics of olanzapine, including in combination with lithium or valproate.^{3,12,13} OSC should

be distinguished from a different combination product, olanzapine-fluoxetine combination (Symbyax, originally manufactured and distributed by Eli Lilly and Company/Lilly USA, LLC, Indianapolis, IN USA), approved for acute depressive episodes associated with bipolar I disorder and for treatment-resistant depression.¹⁴

OSC offers the potential to consider olanzapine earlier in the treatment of schizophrenia or bipolar I disorder, especially among practitioners who might otherwise be hesitant to prescribe this agent because of concerns over the risk of excessive weight gain.

OSC is available in 4 dosage strengths containing 5 mg, 10 mg, 15 mg, or 20 mg of olanzapine; all tablets contain 10 mg of samidorphan.² The recommended starting dose for OSC mirrors the language contained

OSC is intended to mitigate some of the weight gain anticipated when using olanzapine alone

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Samidorphan does not alter the pharmacokinetics of olanzapine, including in combination with lithium or valproate



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Table

Fast facts about olanzapine-samidorphan combination

Brand name: Lybalvi
Class: Olanzapine-samidorphan combination consists of olanzapine, a second-generation antipsychotic, and samidorphan, an opioid antagonist
Indication: Schizophrenia in adults and bipolar I disorder in adults (acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate, and as maintenance monotherapy treatment)
Approval date: May 28, 2021
Availability date: October 2021
Manufacturer: Alkermes, Inc.
Dosing forms: Tablets (olanzapine/samidorphan): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, and 20 mg/10 mg
Recommended dose: Schizophrenia: Initiate at 5 mg/10 mg or 10 mg/10 mg once daily; recommended dosage is 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg. Bipolar I (manic or mixed): For monotherapy, initiate at 10 mg/10 mg or 15 mg/10 mg once daily; recommended dosage is 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily. For adjunctive to lithium or valproate, initiate at 10 mg/10 mg once daily and recommended dosage is 10 mg/10 mg, 15 mg/10 mg or 20 mg/10 mg, once daily. For bipolar I maintenance monotherapy, administer at 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily.

in the legacy olanzapine product label.⁴ For schizophrenia, the recommended initial dose (olanzapine/samidorphan) is 5 mg/10 mg or 10 mg/10 mg once daily. For bipolar I manic or mixed episodes, the recommended starting dose for monotherapy is 10 mg/10 mg or 15 mg/10 mg, and for use with lithium or valproate, 10 mg/10 mg. For all indications, the recommended target dose can be 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg, with 5 mg/10 mg as an additional potential dose for maintenance monotherapy of bipolar I disorder. The maximum dose is 20 mg/10 mg once daily. Because the amount of samidorphan in each tablet is fixed at 10 mg, combining tablets of OSC, or cutting OSC tablets in half, is not advisable.

How it works

Product labeling notes that olanzapine is an atypical antipsychotic, that its efficacy in schizophrenia or bipolar I disorder could be mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism, and that the mechanism of action of samidorphan could be mediated through opioid receptor antagonism.²

The pharmacodynamic profile of olanzapine is complex.² It binds with high affinity to the following receptors: serotonin 5HT2A/2C, 5HT6 (Ki = 4, 11, and 5 nM, respectively), dopamine D1-4 (Ki = 11-31 nM), histamine H1 (Ki = 7 nM), and adrenergic alpha-1 receptors (Ki = 19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin 5HT3 (Ki = 57 nM) and muscarinic M1-5 (Ki = 73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds with low affinity to gamma aminobutyric acid type A (GABA-A), benzodiazepine, and beta-adrenergic receptors (Ki >10 μM). Olanzapine’s muscarinic receptor affinity can explain why olanzapine can be associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Thus, OSC 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; a potential drug-drug interaction can be anticipated with concomitant use of anticholinergic medications.² Other pharmacodynamic drug-drug interactions that can occur with the olanzapine component of OSC include the possibility that diazepam, alcohol, or other CNS-acting drugs may potentiate orthostatic hypotension, and there may be a need to reduce the dosage of concomitantly prescribed antihypertensive drugs in patients being treated for hypertension. Moreover, OSC is not recommended in patients receiving levodopa and dopamine agonists.

Samidorphan binds to the mu-, kappa-, and delta-opioid receptors (Ki = .052, .23, and 2.7 nM, respectively).² Samidorphan is an

antagonist at the mu-opioid receptors with partial agonist activity at kappa- and delta-opioid receptors. A major human metabolite of samidorphan (N-dealkylated) binds to the mu-, kappa-, and delta-opioid receptors ($K_i = .26, 23, \text{ and } 56 \text{ nM}$, respectively), and functions as a mu-opioid receptor agonist. The N-oxide major human metabolite binds to mu-, kappa-, and delta-opioid receptors ($K_i = 8, 110, \text{ and } 280 \text{ nM}$, respectively) and functions as a mu-opioid receptor antagonist. This profile differs from that of other opioid antagonists such as naltrexone.^{15,16}

OSC is not a scheduled drug subject to the Controlled Substances Act. Because samidorphan functions as an opioid antagonist, OSC is contraindicated in patients using opioids or undergoing acute opioid withdrawal.² To avoid precipitating opioid withdrawal, 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, before initiating OSC. In emergency situations when an opioid is required, OSC should be discontinued. Patients who attempt to overcome opioid blockade while receiving OSC by using high or repeated doses of exogenous opioids could experience life-threatening or fatal opioid intoxication. Likewise, patients may have decreased tolerance to opioids if OSC therapy is interrupted or discontinued.

Regarding cardiac electrophysiology, OSC was not observed to prolong the electrocardiogram QTc interval to any clinically relevant extent when tested at doses up to 30 mg/30 mg (1.5 times and 3 times the maximum recommended daily dosage of olanzapine and samidorphan, respectively).¹⁷

Clinical pharmacokinetics

The pharmacokinetics of both olanzapine and samidorphan are linear over the clinical dose range and there is no pharmacokinetic interaction between olanzapine and samidorphan after oral administration of OSC.² Coadministration of OSC with lithium or valproate does not have a clinically significant effect on systemic exposure of lithium or valproate.¹³ OSC steady-state concentrations

of olanzapine and samidorphan are reached within 7 days, with accumulation at steady state being 2-fold for olanzapine and 1.3-fold for samidorphan (at 5 days). Elimination half-life for olanzapine is 35 to 52 hours, and for samidorphan, 7 to 11 hours. Olanzapine is metabolized primarily via UGT1A4 and CYP1A2, whereas samidorphan is primarily metabolized by CYP3A4. Consequently, concomitant use of OSC with strong CYP3A4 inducers is not recommended. The recommendation regarding CYP1A2 modulators and OSC are similar to those for olanzapine²⁴: consider reducing the dosage of the olanzapine component in OSC when used concomitantly with strong CYP1A2 inhibitors, and consider increasing the dosage of the olanzapine component in OSC when used concomitantly with CYP1A2 inducers. Because cigarette smoke contains polycyclic aromatic hydrocarbons that act as CYP1A2 inducers,¹⁸ olanzapine clearance is much higher in smokers than in nonsmokers.² This translates to potentially clinically relevant differences when optimizing the dose. In a study of patients with schizophrenia, olanzapine concentrations were lower in self-reported smokers (16.5, 34.2, and 60.9 ng/mL) than in self-reported nonsmokers (25.6, 43.4, and 113.2 ng/mL) for dosages of 10, 20, and 40 mg/d, respectively.¹⁹ In contrast, samidorphan pharmacokinetics are not affected by smoking status.²

No dose adjustment of OSC is needed in patients with hepatic or renal impairment; however, OSC is not recommended for patients with end-stage renal disease because this has not been specifically studied.²

Efficacy

The efficacy of OSC in the treatment of schizophrenia in adults is supported, in part, by the extensive legacy of studies of orally administered olanzapine.² For OSC specifically, acute efficacy was primarily demonstrated in a randomized, double-blind, phase 3, 4-week study establishing superiority vs placebo in acutely exacerbated patients with schizophrenia.⁸ Mitigation of weight gain was assessed separately in a randomized,

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Olanzapine clearance is much higher in smokers, but samidorphan pharmacokinetics are not affected by smoking status

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Treatment with OSC was associated with statistically significantly less weight gain than treatment with olanzapine

double-blind, phase 3, 24-week study comparing OSC with olanzapine in non-acute outpatients with schizophrenia.¹⁰ Both of these 2 trials were accompanied by 52-week open-label extension studies.^{9,11}

The 4-week study evaluated the antipsychotic efficacy of OSC in 401 patients experiencing an acute exacerbation or relapse of schizophrenia who required inpatient treatment.⁸ Patients were required to have a Positive and Negative Syndrome Scale (PANSS) total score ≥ 80 , with a score ≥ 4 on at least 3 of selected positive symptoms, and a Clinical Global Impression-Severity (CGI-S) score ≥ 4 at baseline and screening. Patients were required to be inpatients for the first 2 weeks of the study, and were encouraged to remain as inpatients for all 4 weeks. Patients were randomized to receive OSC, olanzapine, or placebo. Dosing was once-daily and flexible based on clinical response and tolerability for the first 2 weeks of the study, and fixed thereafter. Patients assigned to OSC could receive 10 mg/10 mg or 20 mg/10 mg, and patients randomized to olanzapine could receive 10 mg or 20 mg. The study compared OSC with placebo, with olanzapine serving as an active control. Treatment with OSC resulted in significant improvements in symptoms compared with placebo at Week 4, as measured by changes in PANSS total scores from baseline. Improvement in PANSS scores with OSC relative to placebo was similar to that observed with olanzapine. The antipsychotic efficacy of OSC relative to placebo was also supported by improvements in CGI-S scores. Thus, the inclusion of samidorphan in OSC did not negatively impact the antipsychotic efficacy of olanzapine.

In the 24-week study, 561 patients were randomized to OSC or olanzapine.¹⁰ There was no placebo control. Patients were treated with doses of OSC 10 mg/10 mg or 20 mg/10 mg, or with doses of olanzapine 10 mg or 20 mg. Dosing was flexible for the first 4 weeks of the study and fixed thereafter. Eligible patients were age 18 to 55 years (younger than the 4-week study, where the maximum age was 70 years), with a body

mass index of 18 to 30 kg/m² (lower than the upper limit of 40 kg/m² used in the 4-week study). In contrast to the acutely exacerbated patients in the 4-week study, patients were required to have a PANSS total score of 50 to 90, CGI-S score ≤ 4 , and symptoms suitable for outpatient treatment. The co-primary endpoints were percent change from baseline in body weight and proportion of patients who gained $\geq 10\%$ body weight at Week 24. Treatment with OSC or olanzapine resulted in similar improvements in PANSS total and CGI-S scores, but treatment with OSC was associated with statistically significantly less weight gain than treatment with olanzapine, and with a smaller proportion of patients who gained $\geq 10\%$ body weight. The least squares mean percent weight change from baseline to the end of treatment was 4.2% with OSC vs 6.6% with olanzapine. Although patients treated with OSC or olanzapine had similar weight gain for the first 4 weeks of treatment, OSC weight gain stabilized after approximately the 6th week, whereas patients who received olanzapine continued to gain weight throughout the remainder of the treatment period. The risk of gaining $\geq 10\%$ body weight from baseline was reduced by 50% with OSC compared with olanzapine. Moreover, the odds of gaining $\geq 7\%$ body weight from baseline at Week 24 were also reduced by 50% for OSC compared with olanzapine. OSC was also associated with smaller increases in waist circumference compared with olanzapine, which was observable as early as Week 1. The risk of experiencing a 5-cm increase in waist circumference was 50% lower for patients treated with OSC vs olanzapine, a relevant threshold in assessing risk of all-cause mortality and cardiovascular disease.²⁰ However, changes in metabolic laboratory parameters in patients treated with OSC or olanzapine were generally small and were similar between groups. In addition, there were little differences between the 2 treatment groups in metabolic parameter changes considered to be of potential clinical significance, based on commonly used thresholds.

Patients on stable, chronic olanzapine therapy were not specifically studied, so the

weight effect of switching from olanzapine to OSC is unknown.

For bipolar I manic or mixed episodes, the use of OSC as monotherapy or in combination with lithium or valproate, as well as for maintenance monotherapy, was approved based on legacy clinical trials with olanzapine, as described in product labeling,²⁴ as well as pharmacokinetic data evidencing that OSC did not have a clinically significant effect on the pharmacokinetics of lithium or valproate.¹³ A study is in progress to evaluate the effect of OSC compared with olanzapine on body weight in young adults with schizophrenia, schizophreniform, or bipolar I disorder who are early in their illness (ClinicalTrials.gov identifier: NCT03187769).

Overall tolerability and safety

The systemic safety and tolerability profile for OSC would be expected to be similar to that for olanzapine, unless there are adverse events that are specifically related to the samidorphan component. In the 4-week acute study described above,⁸ adverse events that occurred at least twice the rate of placebo with OSC included increased weight (18.7%, 14.3%, 3.0%, for OSC, olanzapine, and placebo, respectively), somnolence (9.0%, 9.8%, 2.2%), dry mouth (7.5%, 5.3%, 0.7%), and headache (6.0%, 5.3%, 3.0%). In the 24-week study,¹⁰ which did not have a placebo control, the most commonly reported adverse events ($\geq 10\%$ of patients) were increased weight (24.8% vs 36.2% for OSC vs olanzapine), somnolence (21.2% vs 18.1%), dry mouth (12.8% vs 8.0%), and increased appetite (10.9% vs 12.3%). In both studies, rates of discontinuation due to adverse events were low and similar between groups (in the 4-week study, 1.5% for OSC, 2.3% for olanzapine, and 5.2% for placebo; in the 24-week study, 12.0% for OSC and 9.8% for olanzapine).

In the 2 open-label, phase 3, 52-week extension studies,^{9,11} long-term tolerability was evidenced by low rates discontinuation due to adverse events ($\leq 6\%$). Neither extension study reported any clinically meaningful changes over time in hematology, biochemistry, vital signs, or electrocardiogram

parameters.³ In addition to durability of antipsychotic response as evidenced by sustained improvements in PANSS and CGI-S scores over time, waist circumference and weight remained stable, and the observed long-term changes in weight were consistent with weight changes observed with other second-generation antipsychotics.³ Long-term changes in metabolic laboratory parameter values were small and remained stable, and there was little change in glycosylated hemoglobin (hemoglobin A1c) values, which suggests that glycemic control was maintained with long-term OSC treatment.³ Caveats to consider are that the extension studies were open label without comparators, and they may have selected for patients who responded favorably to OSC treatment in the preceding studies.³

Warnings and precautions in OSC product labeling are generally similar to those for other second-generation antipsychotics,²¹ other than warnings and precautions specifically related to samidorphan being an opioid antagonist, and special mention of “Drug Reaction with Eosinophilia and Systemic Symptoms” and “Anticholinergic (Antimuscarinic) Effects” warnings, which also are contained in the olanzapine legacy label.²⁴

Summary

Olanzapine has a plethora of evidence supporting its robust efficacy profile^{5,6}; however, its use is stymied by an unfavorable weight and metabolic profile.⁷ OSC may help mitigate at least some of the weight gain that would be expected with the use of olanzapine alone in the long-term treatment of patients with schizophrenia or bipolar I disorder. The addition of samidorphan does not deleteriously affect the efficacy of olanzapine, but decreases the risk of gaining $\geq 10\%$ or $\geq 7\%$ of baseline body weight by approximately 50% compared with olanzapine alone. Increase in waist circumference, a proxy for how much metabolically active fat one has, is lower with OSC than it is with olanzapine. Because samidorphan is an opioid receptor antagonist, OSC is contraindicated in patients using

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Longer-term use of OSC is supported by extension studies lasting one year

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Do not prescribe OSC for patients using opioids or those undergoing acute opioid withdrawal

Related Resource

- Olanzapine and samidorphan (Lybalvi) prescribing information. <https://www.lybalvi.com/lybalvi-prescribing-information.pdf>

Drug Brand Names

Diazepam • Valium	Olanzapine-samidorphan combination • Lybalvi
Lithium • Eskalith, Lithobid	Olanzapine • Zyprexa
Olanzapine • Zyprexa	Valproate • Depakote, Depakene
Olanzapine-fluoxetine combination • Symbyax	

opioids and in those undergoing acute opioid withdrawal. Dosage strengths available for OSC parallel those for olanzapine, and all strengths including the same fixed dose of samidorphan—10 mg—so advise patients not to double up on the tablets, and to not split them.

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Bottom Line

Olanzapine-samidorphan combination (OSC) is intended to mitigate some of the weight gain anticipated when using olanzapine alone. For clinicians who have prescribed olanzapine and have seen its therapeutic benefits, OSC will be a welcome addition to the therapeutic armamentarium. For practitioners who may have avoided olanzapine entirely, OSC can provide another means of offering this therapeutic option and counter “olanzapine hesitancy.”