Olanzapine and Samidorphan (Lybalvi®)
FDA approved June 2021
Manufacturer: Alkermes

Indication: Lybalvi, a combination of olanzapine and samidorphan, is indicated for the treatment of Schizophrenia and Bipolar I disorder in adults. It can be used as an acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate as well as maintenance monotherapy

Mechanism of Action: Olanzapine effects are thought to be mediated through a combination of dopamine & serotonin ($5HT_2$) antagonism. Samidorphan is mu-opioid receptor antagonist with partial agonist activity at kappa & delta opioid receptors. Opioid receptor antagonism could explain efficacy of samidorphan

Dosage

Indication	Initial Dose (olanzapine/samidorphan)	Recommended 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

- Renal impairment: Not recommended in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m^2)
- Hepatic impairment: No dosage adjustment necessary

Administration

- Administer once daily with or without food
- Do not divide tablets or combine strengths
- Recommended initial dose 5 mg/10 mg for pts with predisposition to hypotensive reactions, potential for slower olanzapine metabolism, or pharmacodynamically sensitive to olanzapine

Dosage form & strengths
Olanzapine/samidorphan (OLZ/SAM): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, 20 mg/10 mg tabs

Warnings and Precautions

	Olanzapine	Olanzapine & Samidorphan
Black Box Warning	Elderly pts with dementia-related psychosis treated with antipsychotics are at an increased risk of death	
	• When using olanzapine and fluoxetine, refer to Symbyax® PI	
Contraindications	When using olanzapine or Lybalvi® in combination with lithium or valproate, refer to the PI of those products	
	• None with olanzapine monotherapy • When using olanzapine & fluoxetine in combination, refer to Symbyax® PI	• Patients using opioids • Patients undergoing acute opioid withdrawal
Warnings & Precautions	• Increased incidence of cerebrovascular AEs such as stroke, TIA, including fatalities in elderly pts with Dementia-Related Psychosis • Neuroleptic Malignant Syndrome, Hyperprolactinemia, Tardive Dyskinesia, & Seizures • Orthostatic hypotension & syncope • Leukopenia, Neutropenia, and Agranulocytosis • Potential for cognitive & motor impairment	

PI: Package Insert, AE: Adverse Effects, Pts: Patients, Severe Mental Illness (SMI), Triglycerides: TG

	• Use with fluoxetine, lithium or valproate: Also refer to Symbyax, lithium, or valproate PI	

	• Suicide (when using with fluoxetine)
	• Weight gain
	• Hyperglycemia
	• Hyperlipidemia
	• Laboratory Tests
	  o Monitor fasting glucose & lipid profiles
		• Precipitation of opioid withdrawal in pts dependent on opioids. Before starting lybalvi, there should be at least
		  o 7-day opioid-free interval for short-acting opioids
		  o 14-day opioid-free interval for long-acting opioids
		• Vulnerability to life-threatening opioid overdose particularly if lybalvi use is interrupted or discontinued
		  o Risk of overdose from attempts to overcome Lybalvi opioid blockade
		  o Risk of resuming opioids in pts with prior opioid use
		  ▪ may have reduced opioid tolerance if Lybalvi use is interrupted or discontinued
		• Metabolic Changes
		• Drug Reaction with Eosinophilia and Systemic Symptoms
		• Anticholinergic effects

Adverse Effects (≥5% and at least twice that for placebo)	• Schizophrenia: postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia	• Schizophrenia: weight gain, somnolence, dry mouth, & headache
	• Bipolar I Disorder, Manic or Mixed Episodes Olanzapine: asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor • Olanzapine as adjunct to lithium or valproate: dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia	

Drug Interactions

Strong CYP3A4 Inducers	Not recommended
Strong CYP1A2 Inhibitors	Consider dosage reduction of olanzapine component
CYP1A2 Inducer	Consider dosage increase of the olanzapine component
CNS Acting Drugs	May potentiate orthostatic hypotension
Anticholinergic Drugs	Can increase risk for severe GI side effects
Antihypertensive Agents	Monitor BP
Levodopa & Dopamine Agonists	Not recommended

Pharmacokinetics

	Olanzapine	**Samidorphan**
Absolute Oral Bioavailability	Not applicable	69%
Time to peak concentration	4.5 to 7 hours	1 to 2 hours
Steady state	7 days	5 days
$T_{1/2}$	35 to 52 hours	7 to 11 hours
Severe Hepatic Impairment	may be expected to reduce clearance	estimated increase in Cmax: 2.1-fold AUC: 2.3-fold
Excretion	Urine: 57% (unchanged + metabolites) Feces: 30% (unchanged + metabolites)	Urine: 67% (unchanged + metabolites) Feces: 16% (unchanged + metabolites)

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Clinical Trials

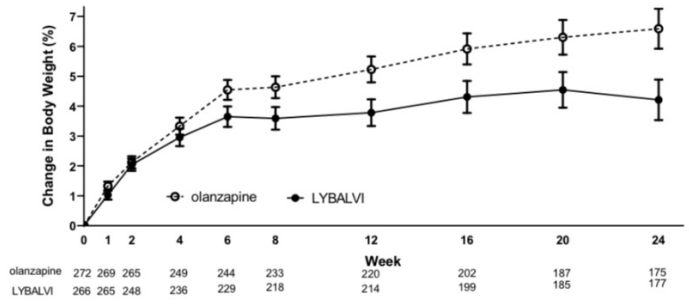
- A randomized double-blind Phase 2 study of olanzapine/samidorphan in pts with schizophrenia found that efficacy of Lybalvi was equivalent and associated with clinically meaningful and statistically significant mitigation of weight gain compared with olanzapine plus placebo. OLZ/SAM was generally well tolerated, with a safety profile comparable to olanzapine plus placebo
- A double-blind randomized Phase 3 Enlighten-2 study of olanzapine/samidorphan compared to olanzapine over 6 months in 561 patients with stable schizophrenia found that the efficacy of OLZ/SAM was similar to olanzapine monotherapy, it was associated with significantly less weight gain & smaller increase in waist circumference
    - primary endpoints were percent change in body weight from baseline & proportion of pts who gained ≥ 10% weight at week 24
    - lower mean percent weight gain from baseline at 6 months (3.2 Vs. 5.1 kg)
    - lower proportion of pts who gained 10% or more of their body weight at 24 weeks (17.8% vs 29.8%)
    - percent change in weight from baseline: 6.6% vs. 4.2% among the OLZ/SAM & olanzapine groups respectively
    - lower proportion of pts who gained 7% or more of their body weight at 24 weeks (27.5% and 42.7%)
    - Metabolic changes were similar
    - Most common AEs (OLZ/SAM compared with olanzapine)
        - weight gain: 24.8% vs 36.2%
          somnolence: 21.2% vs 18.1%
          dry mouth: 12.8% vs 8.0%
          increased appetite: 10.9% vs 12.3%
- Olanzapine efficacy for the treatment of Bipolar 1 Disorder has been previously established. No additional studies were conducted for OLZ/SAM for Bipolar 1 Disorder
- Weight Change Comparison between Olanzapine & Lybalvi from Enlighten-2 long-term extension study

Table 8: Primary Efficacy Results for Change from Baseline in Weight at Week 24 in Patients with Schizophrenia (Study 2)

	% Change From Baseline in Body Weight			≥10% Body Weight Gain	
Treatment Group	Baseline Mean, kg (SD)	LS Mean % Change From Baseline (SE)	Olanzapine-subtracted Difference (95% CI)	Percentage of Patients	Olanzapine-subtracted Risk Difference (95% CI)
LYBALVI (10 mg/10 mg, 20 mg/10 mg) (N=266)	77.0 (13.7)	4.2 (0.7)	-2.4 (-3.9, -0.9)	17.8	-13.7 (-22.8, -4.6)
Olanzapine (10 mg, 20 mg) (N=272)	77.5 (13.5)	6.6 (0.7)	—	29.8	—

Abbreviations: CI: confidence interval; LS: least squares; SD: standard deviation; SE: standard error.

Figure 5: Percent Change from Baseline in Body Weight by Time (Week) in Patients with Schizophrenia (Study 2)



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Role in Therapy

- Samidorphan, a new chemical entity structurally similar to naltrexone with high affinity for mu-opioid receptors, appears to reduce olanzapine induced weight gain
    - not associated with improvements in lab based metabolic endpoints such as cholesterol, TG, glucose, A1C, or insulin
- Olanzapine/samidorphan is contraindicated for use in patients using opioids and those undergoing acute opioid withdrawal. Additional warnings include risks of opioid overdose and precipitation of opioid withdrawal in patients physiologically dependent on opioids
    - pts who experience reduced effects of opioids may try to compensate by taking higher dose leading to potentially fatal complications
- OLZ/SAM may cause less weight gain compared to olanzapine, however, weight gain is still the most common AE
- Results of a phase 3 study to assess 1-year safety & tolerability suggest that OLZ/SAM was generally well tolerated
    - weight, waist circumference, metabolic lab parameters, & schizophrenia sx remained stable
- Other antipsychotics with a lower risk of weight gain include aripiprazole, ziprasidone, asenapine, brexpiprazole, lumateperone, lurasidone, and most high to mid potency 1st generation antipsychotics
- Adjunctive meds to reduce antipsychotic-induced weight gain in pts with severe mental illness (SMI)
    - Bupropion-naltrexone
        - not studied in pts with SMI (use must be considered carefully)
    - Orlistat (pancreatic lipase inhibitor)
        - lack of efficacy in pts on antipsychotics
    - Off-label use
        - Several meds have shown efficacy in studies in SMI patients with antipsychotic-induced weight gain
        - Metformin
            - appears efficacious; mean difference in weight reduction 3.17 kg (95% CI -4.44 to -1.90 kg)
            - generally well tolerated and associated with significant improvements in TGs & A1c
            - common AEs: N/V, diarrhea & abdominal discomfort
              infrequent: headache, myalgia, weakness, low vitamin B12 levels
        - Topiramate
            - not as well studied, but shows evidence of efficacy
            - mean difference in weight reduction 3.17 kg (95% CI -5.55 to -0.73 kg)
            - common AEs: paresthesias, sedation, dizziness, & memory difficulties
            - consider slow titration & moderate dosing
        - Aripiprazole
            - Clinical trials data suggest reduction in weight gain in pts treated with clozapine or olanzapine
            - mean difference 2.13 kg (95% CI -2.87 to -1.39) compared with placebo
            - improved LDL & total cholesterol
            - AEs when taken with clozapine: nausea, anxiety & akathisia
        - Liraglutide
            - Glucagon-like peptide-1 agonist FDA approved for weight loss
            - may be safe & effective for weight loss in overweight/obese individuals with SMI
            - results of a clinical trial suggest that overweight/obese individuals on clozapine or olanzapine with schizophrenia & prediabetes who received liraglutide lost weight while pts in the placebo group had an average weight gain (-4.7 vs +0.5 kg)

- Common AEs include nausea, abdominal discomfort, & diarrhea

Price Comparison
Lybalvi all strengths WAC pricing: $1450
Olanzapine generic all strengths: under $1

Formulary Recommendation
PA required for BHRS, Medi-Cal and CMC

Approval Criteria
All criteria below must be met:

- FDA approved indications prescribed by psychiatrist
- Not on any opioid medications and no known opioid use disorder
- Trial of 2 generic atypical antipsychotics with lower weight gain risk, such as Aripiprazole
- Trial of naltrexone or metformin for weight control during antipsychotic therapy

Quantity Limit #30/30DS, with max dose 20 mg olanzapine/10 mg samidorphan a day

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