Olanzapine and Samidorphan (LYBALVI)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action[1]

- Olanzapine and samidorphan is a combination of an atypical antipsychotic and an opioid receptor antagonist. Olanzapine acts as an antagonist at the dopamine and serotonin type 2 receptors, while samidorphan is an opioid antagonist at the mu receptor.

Indication(s) Under Review in This Document[1]

- 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

Dosage Form(s) Under Review

- Tablets (olanzapine/samidorphan): 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg

Clinical Evidence Summary

Efficacy Considerations[2,3]

- The efficacy of olanzapine/samidorphan (OLZ/SAM) was studied in two phase 3 trials in patients with schizophrenia, one (ENLIGHTEN-1) in patients with an acute exacerbation and the other (ENLIGHTEN-2) in clinically stable outpatients (Table 1).
- ENLIGHTEN-1 (Study 1, NCT#02634346) was a phase 3 randomized, double-blind, active- (olanzapine) and placebo-controlled trial that was conducted over 4 weeks to assess the efficacy of OLZ/SAM in adults experiencing an acute exacerbation of schizophrenia compared to olanzapine monotherapy and placebo (n=403).
    - Most of the patients were Caucasian males with an average age around 41 years old and a mean baseline BMI of 26.6.
    - Participants either received OLZ/SAM (10 mg/10 mg or 20 mg/10 mg) or olanzapine (10 mg or 20 mg) or placebo.

  - The efficacy measures were change in Positive and Negative Syndrome Scale (PANSS) score from baseline to week 4 (primary) and Clinical Global Impressions-Severity of Illness Scale (CGI-S) score from baseline to week 4 (secondary).
  - OLZ/SAM resulted in a significant improvement versus placebo in PANSS total and CGI-S scores from baseline to week 4 (least squares mean +/- SE: -6.4 ± 1.8 and -0.4 +/- 0.1, respectively; Table 2 and Table 3)
  - Olanzapine monotherapy resulted in similar improvement in PANSS and CGI-S scores (least squares mean +/- SE: -5.3 +/- 1.8 and -0.4 +/- 0.1, respectively; Table 2 and Table 3)
  - There was a high placebo response observed at the end of the trial (LS mean improvement in PANSS score -17.5)
- ENLIGHTEN-2 (Study 2, NCT#02694328) was a phase 3 randomized, double-blind trial that was conducted over 24 weeks to evaluate the weight profile of OLZ/SAM in patients with schizophrenia in the outpatient setting compared to olanzapine monotherapy (n=561)
  - Most of the patients were African American males with average age of 40 years old and a mean baseline BMI 25.45
  - Participants either received OLZ/SAM (10 mg/10 mg or 20 mg/10 mg) or olanzapine (10 mg or 20 mg)
  - Efficacy measures were the co-primary endpoints of percent change in body weight from baseline to week 24 and proportion of subjects with $\geq$10% weight gain from baseline to week 24. The secondary endpoint was the proportion of subjects with $\geq$7% weight gain from baseline to week 24. Additionally, waist circumference, fasting triglycerides, cholesterol, glucose, and insulin, along with non-fasting hemoglobin A1c were assessed at each visit (Table 4)
  - Statistically significant less weight gain was seen in those taking OLZ/SAM when compared to olanzapine monotherapy [3.18 kg (OLZ/SAM) vs. 5.08 kg (olanzapine) at week 24] and the weight mitigations is first observed at approximately 6 weeks (Table 4)
  - Changes in metabolic parameters were similar between the OLZ/SAM and olanzapine monotherapy groups (Table 4)
  - Limitations include BMI restriction of 18-30 in patients with long history of illness may have inadvertently included patients relatively resistant to antipsychotic associated weight gain, almost 40% of patients discontinued the study early, and no adherence measures were performed

Table 1: Inclusion and Exclusion Criteria for ENLIGHTEN-1 and ENLIGHTEN-2[2,3]

ENLIGHTEN-1[2]

Inclusion	Exclusion
• Adults aged 18 to 70 years old who met DSM-5 criteria for schizophrenia • Met criteria for an acute exacerbation or relapse of schizophrenia symptoms • A PANSS score of 80 or greater with a score of 4 or more on at least 3 of the following sub-scores: item 1 (delusions), item 2 (conceptual disorganization), item 3 (hallucinatory behavior), and item 6 (suspiciousness/persecution) • A CGI-S score of 4 or more at baseline and screening • BMI of 18 to 40 kg/m^2 • Abide by contraception methods stipulated in the protocol	• Presence of a clinically significant or unstable medical illness, condition or disorder that could potentially compromise patient safety • History of diabetes • Moderate or severe alcohol or drug use disorder currently or during the 3 months prior to screening • A positive urine drug screen for opioids, amphetamine/methamphetamine, phencyclidine, or cocaine at screening • An assessment that the patient was at risk for suicide • Previous exposure to olanzapine, mesoridazine, chlorpromazine, thioridazine, or a long-acting injectable antipsychotic medication within 6 months prior to screening (exception: for 3-month paliperidone must not have received within 12 months of screening) • Initiated first antipsychotic treatment within the past 12 months • Less than a year had elapsed since the initial onset of active-phase schizophrenia symptoms • Received clozapine within 6 months prior to screening • History of clozapine use for treatment-resistant schizophrenia or inadequate response to treatment with olanzapine • Taken an opioid agonist within 14 days or opioid antagonist within 60 days prior to screening • Use of weight-loss or hypoglycemic drugs at screening • Use of a statin if initiated or the dose changed within 3 months of screening

ENLIGHTEN-2[3]	
Inclusion • Adults aged 18 to 55 years old who met DSM-5 criteria for a primary diagnosis of schizophrenia • Baseline BMI between 18-30 • Self-reported stable body weight (≤ 5% change) for at least 3 months before study initiation • Patients in the outpatient setting	**Exclusion** • History of treatment-resistant schizophrenia • Initial symptom onset < 1 year • Antipsychotic naïve • Active alcohol or substance use disorders (excluding marijuana/tetrahydrocannabinol) • Olanzapine use in the 60 days prior to screening • Opioid agonist use within 14 days of screening, opioid antagonist use within 60 days of screening or anticipated need for opioid treatment during study period • Any clinically significant or unstable medical illness that might compromise patient safety (e.g., diabetes, hypo- or hypertension, thyroid dysfunction, and history of seizure disorder or brain tumor), study endpoint or interfere with the ability to fulfill study requirements

BMI: body mass index, CGI-S: clinical global impression-scale, PANSS: positive and negative symptoms scale

Table 2. PANSS results, ENLIGHTEN-1[2]

	OLZ/SAM N=132	Olanzapine N=132	Placebo N=133
PANSS total score at baseline (mean +/- SD)	101.8 +/- 11.6	100.6 +/- 12.1	102.7 +/- 11.9
Change from baseline in PANSS total score (mean +/- SD)	-23.7 +/- 12.6	-22.4 +/- 13.6	-19.4 +/- 14.8
LSM change in PANSS score from baseline (mean +/- SE)	-23.9 +/- 1.3	-22.8 +/- 1.3	-17.5 +/- 1.3
LSM difference +/- SE vs placebo	-6.4 +/- 1.8	-5.3 +/- 1.8	-
P value vs placebo	<0.001	0.004	-

LSM: least squared means, OLZ/SAM: olanzapine/samidorphan, SD: standard deviation, PANSS: positive and negative syndrome scale, SE: standard error

Table 3. CGI-S results, ENLIGHTEN-1[2]

	OLZ/SAM N=132	Olanzapine N=132	Placebo N=133
CGI score at baseline (mean +/- SD)	5.1 +/- 0.7	5.1 +/- 0.7	5.1 +/- 0.7
Change from baseline in CGI total score (mean +/- SD)	-1.2 +/- 0.9	-1.3 +/- 1.0	-0.9 +/- 1.0
LSM change in CGI score from baseline (mean +/- SE)	-1.2 +/- 1.0	-1.3 +/- 1.0	-0.8 +/- 1.0
LSM difference +/- SE vs placebo	-0.4 +/- 0.1	-0.4 +/- 0.1	-
P value vs placebo	0.002	<0.001	-

CGI-S: Clinical Global Impressions-Severity of Illness Scale, LSM: least squared means, OLZ/SAM: olanzapine/samidorphan, SE: standard error, SD: standard deviation

Table 4. Weight and Metabolic Effects, ENLIGHTEN-2[3]

	OLZ/SAM	Olanzapine	p-value
LSM % change in baseline weight to week 24	4.21%	6.59%	0.003
Proportion of patients with weight gain ≥ 10% from baseline	17.8%	29.8%	0.003
Proportion of patients with weight gain ≥ 7% from baseline	27.5%	42.7%	OR 0.50
Proportion of patients with waist circumference increase ≥ 5 cm	26.8%	43.2%	OR 0.47
Mean total cholesterol change from baseline to week 24 (mg/dL)	0.9	2.1	----
Mean HDL change from baseline to week 24 (mg/dL)	-5.1	-4.5	----
Mean LDL change from baseline to week 24 (mg/dL)	0.6	0.9	----
Mean triglycerides change from baseline to week 24 (mg/dL)	23.9	24.5	----
Mean glucose change from baseline to week 24 (mg/dL)	4.5	2.3	----
Mean insulin change from baseline to week 24 (μIU/mL)	3.22	3.40	----
Mean non-fasting HbA_{1c} from baseline to week 24 (%)	0.06	0.07	----

LSM: least squared means, OLZ/SAM: olanzapine/samidorphan, HDL: high density lipoprotein, LDL: low density lipoprotein, HbA_{1c}: hemoglobin A_{1c}, OR: odds ratio, CM: centimeter

Safety Considerations

Table 5. Safety results from ENLIGHTEN-1[2]

Adverse Event*	OLZ/SAM N=134	Olanzapine N=133	Placebo N=134
Weight gain	18.7%	14.3%	3%
Somnolence	9%	9.8%	2.2%
Dry mouth	7.5%	5.3%	0.7%
Anxiety	6%	5.3%	6%
Headache	6%	5.3%	3%
Schizophrenia exacerbation/worsening	0.7%	1.5%	6%

OLZ/SAM: olanzapine/samidorphan
*Adverse events in >5% of patients in any group

Table 6: Safety Results from ENLIGHTEN-2[3]

Adverse Event*	OLZ/SAM N=274	Olanzapine N=276
Weight gain	24.8%	36.2%
Somnolence	21.2%	18.1%
Dry mouth	12.8%	8%
Increased appetite	10.9%	12.3%
Increased weight circumference	6.2%	8%
Increased blood creatinine phosphokinase	5.1%	4.3%

OLZ/SAM: olanzapine/samidorphan
*Adverse events in >5% of patients in any group

Contraindications:

- Patients using opioids
- Patients undergoing acute opioid withdrawal.
- If OLZ/SAM is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for those products.

Other warning/precautions:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis
- Precipitation of Opioid Withdrawal in Patients who are Dependent on Opioids
- Vulnerability to Life-Threatening Opioid Overdose
- Neuroleptic Malignant Syndrome
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Metabolic Changes
- Tardive Dyskinesia
- Orthostatic Hypotension and Syncope
- Falls

- Leukopenia, Neutropenia, and Agranulocytosis
- Seizures
- Potential for Cognitive and Motor Impairment
- Anticholinergic Effects
- Hyperprolactinemia

Other Considerations[1]

Pregnancy

- May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure
    - Pregnancy exposure registry available

Renal Impairment

- Not recommended for use in patients with end-stage renal disease (eGFR of <15 ml/min/1.73 m^2)

Opioid Use or Acute Withdrawal

- Opioid-free interval (7 days for short-acting opioids and 14 days for long-acting opioids) required before initiation
- Increased vulnerability to overdose due to potential increased sensitivity to opioids and attempts to overcome samidorphan's opioid receptor blockade

Interactions

- Use with strong CYP3A4 inducers should be avoided
- Use with levodopa and dopamine agonists should be avoided
- Pharmacokinetic properties of samidorphan are not affected by smoking status or sex

Dosing Limitations

- Max dose of olanzapine available in combination tablet is 20 mg
    - No guidance given on patients requiring more than 20 mg of olanzapine

Patient Identifier

- Similar to other opioid receptor antagonists, it may be recommended for a patient to have a patient identifier with them considering the warning with opioid use and acute withdrawal

Other Therapeutic Options

Table 7. Treatment Alternatives

Drug	Formulary Status	Clinical Guidance	Other Considerations
Olanzapine/ samidorphan	TBD	• Lessens antipsychotic-induced weight gain • Treatment of schizophrenia in adults and bipolar I disorder in adults[1] • Study weight gain endpoint reduced by 50% relative to olanzapine monotherapy[3] • Final weight change at week 24: 3.18 kg (OLZ/SAM) vs. 5.08 kg (olanzapine monotherapy)[3]	• Common adverse effects (>5% of patients exposed and twice the rate of placebo): weight gain, somnolence, dry mouth, and headache[1]
Topiramate	F	• Treatment of antipsychotic induced weight gain (off-label) • Significant weight mitigation compared to antipsychotic monotherapy (15 trials, n=713, mean weight difference: -2.75 kg)[5] • Not recommended for use within guidelines due to side effect profile	• Common adverse effects (>5% more frequent than placebo): paresthesia, anorexia, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, difficulty with memory, concentration problems, cognitive problems, confusion, mood problems, fever, infection, and flushing[6]
Metformin	F	• Treatment of antipsychotic-induced weight gain (off-label)[5] • Statistically significant weight reduction compared to placebo (12 studies, n = 743, mean weight change: -3.27 kg)[11] • Significant reduction in BMI (−1.13 kg/m^2) and insulin-resistance index (−1.49) compared to placebo [11] • No significant reduction in fasting blood glucose [11] • BAP guidelines regarding management of weight gain, metabolic disturbances and cardiovascular risk with antipsychotic treatment recommends metformin should be considered in patients who are at high risk of diabetes, only after lifestyle interventions fully explored[13]	• Only studied as treatment for antipsychotic-induced weight gain, after it occurs • Common adverse effects (>5% more frequent than placebo): diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache [IR form]. Diarrhea, nausea/vomiting [ER form][8]

Naltrexone	F	• No significant change in BMI between olanzapine plus naltrexone (n=14) versus olanzapine alone (n=16) at 12 weeks[14] • Olanzapine plus naltrexone decreased body fat mass and increased fat-free mass at week 12[14] • No significant differences in plasma lipids and liver function tests • Not included in recommendations for treatment or prevention of antipsychotic-induced weight gain	• Common adverse effects (>5% more frequent than placebo) were not noted[14] • Patients treated for opioid addiction have experienced: difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache • Post-marketing pilot trial that included patients that were already on olanzapine • Lower binding affinity for receptors in comparison to samidorphan

BMI: body mass index; ER: extended release; IR: immediate release; OLZ/SAM: olanzapine/samidorphan, BAP: British Association of Psychopharmacology; F: formulary, TBD, to be determined

Projected Place in Therapy

- The lifetime prevalence of schizophrenia is ~1% and leads to large healthcare costs and burden on patients.[9] A 2014 study estimated that about 120,000 veterans who were receiving healthcare within the VA were affected by schizophrenia.[10]
- Weight gain is a possibility with all antipsychotics, but the risk is highest with olanzapine and clozapine. [11] Weight gain is highest in the first 6 months of therapy for all antipsychotics, but continues throughout treatment.[11] A systematic review from 2011 found the average weight gain with olanzapine in antipsychotic naïve patients was 5 to 6 kg by 6 to 8 weeks, 7 to 9 kg by 6 months and 11 to 17 kg at 1 year.[12]
- ENLIGHTEN-1 showed that the addition of samidorphan to olanzapine does not affect the antipsychotic efficacy of olanzapine.[2] ENLIGHTEN-2 showed statistically significant less weight gain in subjects receiving OLZ/SAM when compared to olanzapine monotherapy [3.18 kg (OLZ/SAM) vs. 5.08 kg (olanzapine) at week 24], however, **no significant changes were noted in the other metabolic parameters assessed.[3]**
- Current guidelines on the management of weight gain associated with antipsychotics do not include OLZ/SAM.[13] The proposed alternative options for antipsychotic associated weight gain include metformin and topiramate, however, only metformin is recommended due to topiramate's adverse effect profile.[4-7]
- There are no studies comparing OLZ/SAM to olanzapine plus metformin. The available studies on combining metformin with olanzapine have been done in patients who have already

experienced antipsychotic associated weight gain whereas OLZ/SAM was studied in lessening antipsychotic associated weight gain before it occurs.[2,3,11]

- The most common adverse effects associated with OLZ/SAM are weight gain, somnolence, dry mouth, headache, and increased appetite.[2,3] Additionally, patients cannot be receiving opioids and will need to be assessed and screened for opioid use prior to initiation of OLZ/SAM. It may also be beneficial to provide patients with a medical alert identifier, such as those used with naltrexone products.
- The most common side effects associated with metformin include diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.
- **There is no evidence that switching to OLZ/SAM from another antipsychotic will prevent further weight gain or promote weight loss**. [2,3] The patients most likely to benefit from OLZ/SAM are those where olanzapine is indicated based on individual patient characteristics and the patient is at high risk for weight gain, understanding the clinical trials showed no change in metabolic parameters.[3]

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