BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

LYBALVI™ (olanzapine and samidorphan) Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Lybalvi (olanzapine and samidorphan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Individual meets most current version Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for Schizophrenia

    b. Individual meets most current version Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for Bipolar I disorder for:

i. Acute treatment of manic or mixed episode used either as monotherapy and as adjunct to lithium or valproate
ii. Maintenance monotherapy

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Fasting blood glucose
    b. Fasting lipid profile
    c. Weight
    d. **For Schizophrenia**:
        i. Positive and Negative Syndrome Scale (PANSS) total score of at least 50 or more
        ii. Body weight has increased by 5% or more or has gain at least 5 kg or more over the last 3 months while on olanzapine
    e. **For Bipolar I Disorder**: Young Mania Rating Scale (Y-MRS) total score of 16 or more

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. **ONE** of the following:
    a. **For Schizophrenia**: Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **TWO** of the following:
        i. Aripiprazole
        ii. Risperidone
        iii. Olanzapine
    b. **For Bipolar I Disorder**: Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **TWO** of the following:
        i. Lithium (or valproate)
        ii. Aripiprazole
        iii. Quetiapine
        iv. Risperidone
        v. Olanzapine

7. There are **NO** FDA-label contraindications such as:
    a. Individual using opioids
    b. Individual undergoing acute opioid withdrawal
    c. When used with lithium or valproate the individual has no contraindications for these agents

8. Individual does not have **ANY** of the following:
    a. Dementia-related psychosis
    b. Recent history of myocardial infarction or unstable cardiovascular disease
    c. End-stage renal disease (estimated glomerular filtration rate less than 15 mL/min/1.73 m^2)

9. Individual who is opioid dependent has not had a short-acting opioid in the last 7-days or a long-acting opioid in the last 14-days

10. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation as follows:

a. Use with strong CYP3A4 inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort and others
b. Use with levodopa and dopamine agonists such as pramipexole, ropinirole, rotigotine

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Lybalvi (olanzapine and samidorphan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Psychiatrist

2. Individual's condition has responded while on therapy with response defined as the following:
   a. **For Schizophrenia**:
      i. Has not gained weight or weight gain is not more than 2 kg
      ii. There is at least a 20% improvement in the Positive and Negative Syndrome Scale (PANSS) total score over baseline
      iii. Clinical Global Impression of Severity (CGI-S) or Clinical Global Impression of Improvement (CGI-I) score of 2 or less
   b. **For Bipolar I Disorder**: There is a decrease in the Young Mania Rating Scale (Y-MRS) total score to 12 or less

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
   a. Neuroleptic malignant syndrome (NMS)
   b. Drug reaction with eosinophilia and systemic symptoms (DRESS)
   c. Tardive dyskinesia, unless it is clinically appropriate to continue Lybalvi
   d. Leukopenia, neutropenia, agranulocytosis in the absence of other causes
   e. Absolute neutrophil count of less than $1000/mm^3$

6. Individual does not have **ANY** of the following:
   a. Dementia-related psychosis
   b. Recent history of myocardial infarction or unstable cardiovascular disease
   c. End-stage renal disease (estimated glomerular filtration rate less than 15 mL/min/1.73 m^2)

7. Individual who is opioid dependent has not had a short-acting opioid in the last 7-days or a long-acting opioid in the last 14-days

8. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation as follows:

a. Use with strong CYP3A4 inducers such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort and others
b. Use with levodopa and dopamine agonists such as pramipexole, ropinirole, rotigotine

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Lybalvi is a combination of olanzapine, an atypical antipsychotic, and samidorphan, a mu-opioid receptor antagonist, indicated for the treatment of schizophrenia in adults and bipolar I disorder in adults for the acute treatment of manic or mixed episodes as monotherapy or as adjunct to lithium or valproate and as maintenance monotherapy treatment. Lybalvi (olanzapine and samidorphan) **is not approved** for the treatment of patients with dementia-related psychosis.

The mechanism of action of olanzapine is unclear; however, its efficacy in the treatment of schizophrenia or bipolar I disorder could be mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of samidorphan could be mediated through opioid receptor antagonism; it has partial agonist activity at kappa- and delta-opioid receptors. Samidorphan is 3-carboxamido-4-hydroxynaltrexone.

The package label describes the effect of Lybalvi on weight. In a 4-week placebo-controlled study, designed to compare Lybalvi with placebo and not with olanzapine alone, in adult patients with schizophrenia, mean changes in weight, and proportion of patients with ≥7% weight increase, were greater in patients treated with Lybalvi and olanzapine than in patients on placebo. In the study, mean weight gain was 3.0 kg in patients treated with Lybalvi, 2.4 kg in patients treated with olanzapine, and 0.2 kg in patients treated with placebo. The proportion of patients with ≥7% weight increase was 26% in patients treated with Lybalvi, 20% in patients treated with olanzapine, and 5% in patients treated with placebo. In a 24-week trial comparing Lybalvi to olanzapine, Lybalvi-treated patients gained on average 4.2% of baseline body weight compared to 6.6% for the olanzapine group, representing a -2.4% treatment effect in favor of Lybalvi. The proportion of patients treated with Lybalvi with ≥10% body weight gain was 17.8% compared to 29.8% for the olanzapine group, representing a -13.7% treatment effect in favor of Lybalvi. Individuals with diabetes were excluded in the study and patients on stable, chronic olanzapine therapy were not specifically studied, so the weight effect of switching from olanzapine to Lybalvi is unknown.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Positive and Negative Syndrome Scale (PANSS):

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.

Positive scale:

7 Items, (minimum score = 7, maximum score = 49)

- Delusions
- Conceptual disorganization
- Hallucinations
- Excitement
- Grandiosity
- Suspiciousness/persecution
- Hostility

Negative scale:

7 Items, (minimum score = 7, maximum score = 49)

- Blunted affect
- Emotional withdrawal
- Poor rapport
- Passive/apathetic social withdrawal
- Difficulty in abstract thinking
- Lack of spontaneity and flow of conversation
- Stereotyped thinking

General Psychopathology scale:

16 Items, (minimum score = 16, maximum score = 112)

- Somatic concern
- Anxiety
- Guilt feelings
- Tension
- Mannerisms and posturing
- Depression
- Motor retardation
- Uncooperativeness
- Unusual thought content
- Disorientation
- Poor attention
- Lack of judgment and insight
- Disturbance of volition
- Poor impulse control
- Preoccupation
- Active social avoidance

PANSS Total score minimum = 30, maximum = 210

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Clinical Global Impression (CGI):

CGI is a 3-item observer-rated scale that measures illness severity (CGI-S), global improvement or change (CGI-C) and therapeutic response. The illness severity and improvement sections of the instrument are used more frequently than the therapeutic response section in both clinical and research settings

CGI-Severity 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. Scores range from 1 (normal, not at all ill) to 7 (extremely ill).

Clinical Global Impression – Severity (CGI-S)	
Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?	
0 = Not assessed	4 = Moderately ill
1 = Normal, not at all ill	5 = Markedly ill
2 = Borderline mentally ill	6 = Severely ill
3 = Mildly ill	7 = Among the most extremely ill patients

Clinical Global Impression – Improvement (CGI-I)	
Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment. Compared to the patient's condition at baseline, how much has changed?	
0 = Not assessed	4 = No changes
1 = Very much improved	5 = Minimally worse
2 = Much improved	6 = Much worse
3 = Minimally improved	7 = Very much worse

Young Mania Rating Scale (Y-MRS):

Y-MRS, is an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score) where higher scores indicate more severe mania, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in manic symptoms. Total score ≤ 12 indicates remission; 13-19 = minimal symptoms; 20-25 = mild mania, 26-37 = moderate mania, 38-60 = severe mania.

	Specify **ONE** of the reasons listed by indicating the number that describes severity
1	Elevated Mood 0 = Absent 1 = Mildly or possibly increased on questioning 2 = Definite subjective elevation; optimistic, self-confident, cheerful; appropriate to content 3 = Elevated, inappropriate to content; humorous 4 = Euphoric; inappropriate laughter; singing
2	Increased Motor Activity Energy 0 = Absent 1 = Subjectively increased 2 = Animated; gestures increased 3 = Excessive energy; hyperactive at times; restless (can be calmed) 4 = Motor excitement; continuous hyperactivity (cannot be calmed)
3	Sexual Interest 0 = Normal; not increased 1 = Mildly or possibly increased 2 = Definite subjective increase on questioning 3 = Spontaneous sexual content; elaborates on sexual matters; hypersexual by self report 4 = Overt sexual acts (towards patients, staff, or interviewer)
4	Sleep

	0 = Reports no decrease in sleep 1 = Sleeping less than normal amount by up to one hour 2 = Sleeping less than normal amount by more than one hour 3 = Reports decreased need for sleep 4 = Denies need for sleep
5	Irritability 0 = Absent 2 = Subjectively increased 4 = Irritable at times during interview; recent episodes of anger or annoyance on ward 6 = Frequently irritable during interview; short; curt throughout 8 = Hostile, uncooperative; interview impossible
6	Speech (rate and amount) 0 = No increase 2 = Feels talkative 4 = Increased rate or amount at times; verbose at times 6 = Push; consistently increased rate and amount; difficult to interrupt 8 = Pressured; uninterruptible; continuous speech
7	Language-Thought Disorder 0 = Absent 1 = Circumstantial; mildly distractibility; quick thoughts 2 = Distractible; loses goal of thought; changes topics frequently; racing thoughts 3 = Flight of ideas; tangentiality; difficult to follow; rhyming; echolalia 4 = Incoherent; communication impossible
8	Content 0 = Normal 2 = Questionable plans, new interests 4 = Special project(s); hypereligious 6 = Grandiose or paranoid ideas; ideas of reference 8 = Delusions; hallucinations
9	Disruptive-Aggressive Behavior 0 = Absent; cooperative 2 = Sarcastic; loud at times, guarded 4 = Demanding; threats on ward 6 = Threatens interviewer; shouting; interview difficult 8 = Assaultive; destructive; interview impossible
10	Appearance 0 = Appropriate dress and grooming 1 = Minimally unkempt 2 = Poorly groomed; moderately disheveled; overdressed 3 = Disheveled; partly clothed; garish make-up 4 = Completely unkempt; decorated; bizarre garb
11	Insight 0 = Present; admits illness; agrees with need for treatment 1 = Possibly ill 2 = Admits behavior change; but denies illness 3 = Admits possible change in behavior; but denies illness 4 = Denies any behavior change

Comparison of DSM-5 criteria for bipolar I disorder and bipolar II disorder

	Bipolar I disorder	Bipolar II disorder
Manic episode(s)	Yes	No

Hypomanic episode(s)	Commonly occur, but not required	Yes
Major depressive episode(s)	Usually occur, but not required	Yes
Mixed features	May occur	May occur
Anxious distress	May occur	May occur
Rapid cycling	May occur	May occur
Psychotic features	May occur	May occur
Catatonia	May occur	May occur

Resources:

Lybalvi (olanzapine and samidorphan) product information, revised by Alkermes, Inc. 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 26, 2024.

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