LOUISIANA BLUE

Select Antipsychotic Drugs

Policy # 00707
Original Effective Date: 07/13/2020
Current Effective Date: 07/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider select antipsychotic drugs, including, but not limited to Secuado®‡ (asenapine), Lybalvi™‡ (olanzapine and samidorphan), Quetiapine 150 mg tablet, Cobenfy™‡ (xanomeline and trospium chloride), and Opipza™‡ (aripiprazole film) to be **eligible for coverage**** when the below patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility will be considered for select antipsychotic drugs, including, but not limited to Secuado (asenapine), Lybalvi (olanzapine and samidorphan), Quetiapine 150 mg tablet, Cobenfy (xanomeline and trospium chloride), and Opipza (aripiprazole film) when the following criteria are met for the requested drug:

- **Requested drug is Secuado:**
  - Patient has a diagnosis of schizophrenia; AND
  - Patient is 18 years of age or older; AND
  - Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO formulary alternatives unless there is clinical evidence or patient history that suggests the use of formulary alternatives to treat schizophrenia will be ineffective or cause an adverse reaction to the patient. Examples of formulary alternatives include aripiprazole, Rexulti®‡ (brexpiprazole), Vraylar®‡ (cariprazine), paliperidone, olanzapine, quetiapine, risperidone, Fanapt®‡ (iloperidone), Latuda®‡ (lurasidone), Caplyta™‡ (lumateperone), clozapine, and ziprasidone.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- **Requested drug is Lybalvi:**
  - Patient is 18 years of age or older; AND
  - Patient is not currently using opioids; AND
  - Patient meets ONE of the following:
    - Patient has a diagnosis of schizophrenia AND

- ❖ Patient has tried and failed (e.g., intolerance or inadequate response) TWO alternative formulary drugs for the treatment of schizophrenia for at least 4 weeks EACH unless there is clinical evidence or patient history that suggest the use of the alternatives will be ineffective or cause an adverse reaction to the patient. Examples of alternative formulary drugs include aripiprazole, Rexulti (brexpiprazole), olanzapine, quetiapine, Fanapt (iloperidone), paliperidone, risperidone, Latuda (lurasidone), Vraylar (cariprazine), Caplyta™‡ (lumateperone), ziprasidone, and clozapine; OR
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- Patient has a diagnosis of bipolar I disorder and meets BOTH of the following:
  - ❖ Patient has tried and failed (e.g., intolerance or inadequate response) lithium or valproic acid after at least 4 weeks unless there is clinical evidence or patient history that suggests the use of lithium or valproic acid will be ineffective or cause an adverse reaction to the patient; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - ❖ Patient has tried and failed (e.g., intolerance or inadequate response) at least one formulary antipsychotic drug for at least 4 weeks unless there is clinical evidence or patient history that suggests the formulary antipsychotic drugs will be ineffective or cause an adverse reaction to the patient. Examples of formulary antipsychotic drugs include aripiprazole, Rexulti (brexpiprazole), olanzapine, quetiapine, Fanapt (iloperidone), paliperidone, risperidone, Latuda (lurasidone), Vraylar (cariprazine), ziprasidone, and clozapine.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- **Requested drug is Quetiapine 150 mg tablet:**
  - Patient has been receiving quetiapine using a different strength tablet; AND
  - Patient is unable to achieve the desired dose of quetiapine using the generically available quetiapine products.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- **Requested drug is Cobenfy:**
  - Patient has a diagnosis of schizophrenia; AND
  - Patient is ≥ 18 years of age; AND

- Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO generic antipsychotic drugs unless there is clinical evidence or patient history that suggests the use of the available generic alternatives will be ineffective or cause an adverse reaction to the patient. Examples of generic antipsychotics include aripiprazole, olanzapine, ziprasidone, paliperidone er, risperidone, haloperidol, and quetiapine.
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- **Requested drug is Opipza:**
  - Patient meets ONE of the following:
    - Patient has a diagnosis of schizophrenia AND is ≥ 13 years of age; OR
    - Patient will use Opipza as adjunctive treatment for major depressive disorder (MDD) AND is ≥ 18 years of age; OR
    - Patient will use Opipza for the treatment of irritability associated with autistic disorder AND is a pediatric patient ≥ 6 years of age; OR
    - Patient has a diagnosis of Tourette's disorder AND is a pediatric patient ≥ 6 years of age; AND
  - There is clinical evidence or patient history that suggests the use of a generically available oral aripiprazole product (e.g., aripiprazole tablet, aripiprazole solution, aripiprazole orally disintegrating tablet) will be/was ineffective or will/did cause an adverse reaction to the patient.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Secuado (asenapine), and Lybalvi (olanzapine and samidorphan) for the treatment of schizophrenia when the patient has NOT tried and failed at least TWO formulary alternatives to be **not medically necessary.****

Based on review of available data, the Company considers the use of Lybalvi (olanzapine and samidorphan) for the treatment of bipolar I disorder when the patient has not tried and failed lithium or valproic acid to be **not medically necessary.****

Based on review of available data, the Company considers the use of Quetiapine 150 mg tablet when the patient is able to achieve the desired dose using a generic quetiapine product to be **not medically necessary.****

Based on review of available data, the Company considers the use of Cobenfy when the patient has not tried and failed at least TWO generic antipsychotic drugs to be **not medically necessary.****

Based on review of available data, the Company considers the use of Opipza (aripiprazole film) when there is an absence of clinical evidence or patient history that suggests the use of a generically available oral aripiprazole product will be ineffective or cause an adverse reaction to the patient to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of Secuado (asenapine), Lybalvi (olanzapine and samidorphan), Quetiapine 150 mg tablet, Cobenfy (xanomeline and trospium chloride) and Opipza (aripiprazole film) when the patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Schizophrenia is a psychiatric disorder involving chronic or recurrent psychosis. Symptoms are classified as either "positive" or "negative." Positive symptoms include hallucinations or delusions, while negative symptoms include a flat affect. Of course, these symptoms are coupled with social and occupational impairments. The treatment of choice for schizophrenia is an antipsychotic medication. Drug examples include aripiprazole, paliperidone, olanzapine, quetiapine, risperidone, and ziprasidone.

Bipolar disorder is a condition marked by episodes of mania, hypomania, and major depression. It can be classified into two subtypes: bipolar I disorder which consists of manic episodes and often hypomanic and depressive episodes, and bipolar II disorder which consists of hypomanic and depressive episodes without manic episodes. These recurrent mood episodes can be life threatening and warrant long-term maintenance pharmacotherapy. There are many options for treatment including lithium, valproate, quetiapine, lamotrigine, aripiprazole, olanzapine, and risperidone. Bipolar major depression is often treated with drugs such as quetiapine, Latuda (lurasidone), olanzapine, and the previously mentioned antimanic drugs.

This policy addresses two new drugs for the treatment of schizophrenia and bipolar disorder: Secuado, and Lybalvi.

Secuado is a topical atypical antipsychotic which demonstrated modest efficacy in an unpublished trial in patients with schizophrenia. Its approval relied upon the efficacy data of a drug containing the same active ingredient, asenapine. There is a lack of head to head data versus other available antipsychotic agents. While the patch gives another alternative for therapy, it is associated with safety issues (including warnings regarding the application of external heat and application site reactions).

Lybalvi is a combination product containing olanzapine and the opioid receptor antagonist, samidorphan. The addition of samidorphan is designed to attenuate the weight-gain associated with olanzapine. The short-term (4-week) pivotal trial of this product demonstrated similar efficacy between Lybalvi and olanzapine in adults with schizophrenia; both agents were superior to placebo. This trial was not designed to evaluate differences in weight gain between the groups. An additional 24-week trial did evaluate the differences in weight gain and found significantly less weight gain with Lybalvi vs olanzapine in adults with schizophrenia. However, the olanzapine-subtracted difference in weight gain was -2.4%, which equates to an approximate 5-pound difference considering the average patient weight. It should be noted that patients in both groups gained weight overall, although the increases were smaller among patients randomized to Lybalvi. An additional limitation with this product is the warning regarding opioid use/withdrawal. Because it contains an opioid receptor antagonist, Lybalvi cannot be used in patients using opioids. It is also only available in limited fixed dose combinations which may not allow the patient to get the ideal dose of olanzapine for their condition. Given these limitations and the small potential benefit of Lybalvi, other antipsychotics may provide a more efficacious and economical option for patients.

This policy also addresses the branded Quetiapine 150 mg tablet. Because quetiapine is available generically in numerous formulations (including 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg immediate release tablets and 150 mg, 200 mg, 300 mg, and 400 mg extended release tablets), this particular product likely does not provide any advantages over the existing products.

This policy also addresses Cobenfy, a combination of xanomeline and trospium chloride that is indicated for the treatment of schizophrenia in adults. Although the mechanism of action of this product is novel, it has the disadvantage of requiring twice daily oral dosing with titration to achieve the recommended dose. Additionally, studies have not been conducted to compare Cobenfy to other available antipsychotic products that have historically been used to treat schizophrenia. Given these limitations, other antipsychotics may provide a more efficacious and economical option for patients.

Finally, this policy addresses Opipza which is an oral film formulation of the atypical antipsychotic, aripiprazole. It was approved pursuant to section 505 (b) based on the following controlled studies of another oral aripiprazole product:

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in pediatric patients ages 13 to 17 years with schizophrenia
- Two short-term trials in adult patients with MDD who had an inadequate response to antidepressant therapy during the current episode
- Two short-term trials in pediatric patients ages 6 to 17 years for the treatment of irritability associated with autistic disorder
- Two short-term trials in pediatric patients ages 6 to 18 years with Tourette's disorder

Based on the review of available data, there is no advantage to the use of Opipza (aripiprazole film) over the traditional, more cost effective dosage forms of aripiprazole.

All medications targeted by this policy are considered alternatives for medications that already exist on the market today.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Secuado was approved in late 2019 for the treatment of schizophrenia in adult patients.

Lybalvi was approved in May 2021 for the treatment of schizophrenia in adults, acute treatment of manic or mixed episodes and bipolar I disorder in adults as monotherapy and as adjunct to lithium or valproate, and maintenance treatment of bipolar I disorder in adults as monotherapy.

Cobenfy was approved in September 2024 for the treatment of schizophrenia in adults.

Opipza was approved in July 2024 for treatment of schizophrenia in patients ages 13 years and older, as adjunctive treatment of major depressive disorder (MDD) in adults, for treatment of irritability associated with autistic disorder in pediatric patients 6 years and older, and for treatment of Tourette's disorder in pediatric patients 6 years and older.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

This policy addresses new antipsychotic agents that do not bring any unique clinical advantages to the existing array of antipsychotic drugs that are available on the market. Given the lack of head to head data with these products compared to existing antipsychotic medications, Secuado, Lybalvi, Quetiapine 150 mg tablets, Cobenfy, and Opipza are considered alternatives to already existing antipsychotic medications on the market today.

References

1. Secuado [package insert]. Hisamitsu Pharmaceutical Company. Japan. Updated October 2019.
2. Secuado Drug Evaluation. Express Scripts. Updated December 2019.
3. Lybalvi [package insert]. Alkermes, Inc. Waltham, MA. Updated May 2021.
4. Lybalvi Drug Evaluation. Express Scripts. Updated July 2021.
5. Bipolar disorder in adults: Choosing maintenance treatment. UpToDate. January, 2022.
6. Bipolar major depression in adults: Choosing treatment. UpToDate. August, 2021.
7. Quetiapine Fumarate [package insert]. Rising Pharma Holdings, Inc. East Brunswick, NJ. Updated March 2022.
8. Opipza [package insert]. Carwin Pharmaceutical Associate, LLC. Hazlet, NJ. Updated January 2025.

9. Cobenfy [package insert]. Bristol-Myers Squibb. Princeton, NJ. Updated September 2024.
10. Cobenfy (xanomeline and trospium chloride) New Drug Review. IPD Analytics. Updated October 2024.

Policy History

Original Effective Date: 07/13/2020
Current Effective Date: 07/01/2025

06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. New policy.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Added new drug, Lybalvi, to policy with relevant criteria and background information and updated criteria to reflect new indication for Caplyta. Also updated criteria for all drugs to include formulary brands as alternatives to try and fail prior to the requested drug.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Added new Quetiapine 150 mg product with relevant criteria and background information.
02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2025	Medical Policy Committee review
02/12/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2025	Medical Policy Committee review
04/09/2025	Medical Policy Implementation Committee approval. Added Cobenfy and Opipza to the policy with relevant criteria and background information.
06/05/2025	Medical Policy Committee review
06/11/2025	Medical Policy Implementation Committee approval. Removed Caplyta from policy as it no longer requires prior authorization. Added Caplyta as an option for patients to try and fail prior to use of Lybalvi or Secuado.

Next Scheduled Review Date: 06/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.