odevixibat (Bylvay™)

Policy # 00783
Original Effective Date: 05/09/2022
Current Effective Date: 05/01/2025

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.*

Progressive Familial Intrahepatic Cholestasis

Based on review of available data, the Company may consider odevixibat (Bylvay™)‡ for the treatment of pruritus due to progressive familial intrahepatic cholestasis (PFIC) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for odevixibat (Bylvay) for the treatment of pruritus due to progressive familial intrahepatic cholestasis will be considered when the following criteria are met:

Initial:

- Patient has a diagnosis of pruritus due to progressive familial intrahepatic cholestasis (PFIC) Types 1 or 2; AND
  *(Note: This specific patient selection criterion is partially an additional Company requirement for coverage eligibility. Requests for Type III or Type IV PFIC will be denied as not medically necessary** if not met).*
- Patient meets one of the following, which confirms the diagnosis of PFIC:
  - Type 1: Presence of mutations in the *ATP8B1* gene; OR
  - Type 2: Presence of mutations in the *ABCB11* gene; AND
- Patient has the presence of moderate to severe pruritus (per the prescriber); AND
  *(Note: This specific patient selection criterion is partially an additional Company requirement for coverage eligibility. Requests for pruritus severity that are not considered moderate to severe will be denied as not medically necessary** if not met).*
- Patient is 3 months of age or older; AND
- Patient has a serum bile acid concentration above the upper limit of the normal reference range for the reporting laboratory; 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 does NOT have a pathologic variant of the *ABCB11* gene that predicts non-function or complete absence of bile salt export pump protein (BSEP-3); AND

- Patient has NOT experienced any of the following: cirrhosis, portal hypertension, or history of a hepatic decompensation event (for example: variceal hemorrhage, ascites, hepatic encephalopathy); AND
- Patient has NOT had a liver transplant; 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).*
- Dose of the requested medication will NOT exceed 6 mg (6,000 micrograms) per day; AND
- Dose of the requested medication will NOT exceed 120 micrograms per kilogram per day; AND
- Patient meets one of the following:
  - If the oral pellets are being requested: patient weighs less than 19.5 kg (43 lbs.); OR
  - If the capsules are being requested: patient weighs 19.5 kg or more; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) BOTH GENERIC ursodeoxycholic acid AND GENERIC cholestyramine or colestipol unless there is clinical evidence or patient history that suggests the use of these products 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) one of the following: GENERIC rifampin, GENERIC naltrexone, or GENERIC sertraline, unless there is clinical evidence or patient history that suggests the use of these products 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 will not use Bylvay in combination with maralixibat (Livmarli™)‡.

Continuation:

- Patient received an initial approval for the requested medication; AND
- Patient has NOT experienced any of the following: cirrhosis, portal hypertension, or history of a hepatic decompensation event (for example: variceal hemorrhage, ascites, hepatic encephalopathy); AND
- Patient has NOT had a liver transplant; 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).*
- Dose of the requested medication will NOT exceed 6 mg (6,000 micrograms) per day; AND
- Dose of the requested medication will NOT exceed 120 micrograms per kilogram per day; AND
- Patient meets one of the following:
  - If the oral pellets are being requested: patient weighs less than 19.5 kg (43 lbs.); OR
  - If the capsules are being requested: patient weighs 19.5 kg or more; AND

- Patient has responded to therapy with the requested medication (e.g., decreased pruritus and/or decrease in serum bile acids); 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 will not use Bylvay in combination with maralixibat (Livmarli).

Alagille Syndrome

Based on review of available data, the Company may consider odevixibat (Bylvay) for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for odevixibat (Bylvay) for the treatment of cholestatic pruritus in patients with Alagille syndrome will be considered when the following criteria are met:

Initial:

- Patient has a diagnosis of cholestatic pruritus due to Alagille syndrome; AND
- Alagille syndrome diagnosis has been confirmed by genetic testing demonstrating *JAG1* or *NOTCH2* deletion or mutations; AND
- Patient is 12 months of age or older; AND
- Patient has the presence of moderate to severe pruritus (per the prescriber); AND
  *(Note: This specific patient selection criterion is partially an additional Company requirement for coverage eligibility. Requests for pruritus severity that are not considered moderate to severe will be denied as not medically necessary** if not met).*
- Patient's serum bile acid concentration is above the upper limit of normal reference range for the reporting laboratory; 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 does NOT have cirrhosis; AND
- Patient does NOT have portal hypertension; AND
- Patient does NOT have a history of a hepatic decompensation event (examples include variceal hemorrhage, ascites, hepatic encephalopathy); AND
- Patient has NOT had a liver transplant; 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).*
- Dose of the requested medication will NOT exceed 7.2 mg (7,200 micrograms) per day; AND
- Dose of the requested medication will NOT exceed 120 micrograms per kilogram per day; AND

- Patient meets one of the following:
  - If the oral pellets are being requested: patient weighs less than 19.5 kg (43 lbs.); OR
  - If the capsules are being requested: patient weighs 19.5 kg or more; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) TWO other systemic medications for Alagille syndrome unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient. Note that examples of systemic medications for Alagille syndrome include cholestyramine, rifampin, and ursodiol; 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) maralixibat (Livmarli) unless there is clinical evidence or patient history that suggests the use of this product 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 will NOT use Bylvay in combination with maralixibat (Livmarli).

Continuation:

- Patient has received an initial approval for the requested medication; AND
- Patient does NOT have cirrhosis; AND
- Patient does NOT have portal hypertension; AND
- Patient does NOT have a history of a hepatic decompensation event (examples include variceal hemorrhage, ascites, hepatic encephalopathy); AND
- Patient has NOT had a liver transplant; 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)*
- Dose of the requested medication will NOT exceed 7.2 mg (7,200 micrograms) per day; AND
- Dose of the requested medication will NOT exceed 120 micrograms per kilogram per day; AND
- Patient meets one of the following:
  - If the oral pellets are being requested: patient weighs less than 19.5 kg (43 lbs.); OR
  - If the capsules are being requested: patient weighs 19.5 kg or more; AND
- Patient has responded to therapy with the requested medication (e.g., decreased pruritus and/or decrease in serum bile acids); 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 will not use Bylvay in combination with maralixibat (Livmarli).

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of odevixibat (Bylvay) when the patient has Type III or Type IV progressive familial intrahepatic cholestasis (PFIC) to be **not medically necessary.****

Based on review of available data, the Company considers the use of odevixibat (Bylvay) when the patient does NOT have pruritus that is considered to be moderate to severe to be **not medically necessary.****

Based on review of available data, the Company considers the use of odevixibat (Bylvay) when the patient has NOT tried and failed other required medications for the condition to be **not medically necessary.****

Based on review of available data, the Company considers the use of odevixibat (Bylvay) when the patient does NOT have a serum bile acid concentration above the upper limit of the normal reference range for the reporting laboratory to be **not medically necessary.****

Based on review of available data, the Company considers the use of odevixibat (Bylvay) when the patient has had a liver transplant to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of odevixibat (Bylvay) when the patient has NOT responded to therapy with the requested medication 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 odevixibat (Bylvay) when patient selection criteria are not met (except the criteria denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Bylvay is an ileal bile acid transporter (IBAT) inhibitor indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC) and for the treatment of cholestatic pruritus in patients 12 months of age and older with Alagille syndrome (ALGS). In PFIC, the recommended dosage is 40 mcg/kg once daily in the morning with a meal. If there is no improvement after 3 months, the dosage may be increased in 40 mcg/kg increments up to 120 mcg/kg once daily not to exceed a total daily dose of 6 mg. The recommended dosage for

patients with ALGS is 120 mcg/kg taken orally once daily in the morning with a meal. A dose reduction to 40 mcg/kg per day may be considered if tolerability issues occur. Dosing should be increased to 120 mcg/kg per day once tolerability issues stabilize. The maximum recommended daily dose for patients with ALGS is 7.2 mg.

PFIC is a group of rare, genetic disorders that affects bile acid transporters. There are currently 4 types of PFIC: Types I, II, III, and IV. An in-depth analysis of each type is beyond the scope of this medical policy. Bylvay clinical studies included Types I and II PFIC. These two types of PFIC are caused by mutations in the *ATP8B1* and *ABCB11* genes, respectively. As a result of the mutations, retention of bile acids occur within the body. Bile flow is integral for the digestion and absorption of dietary fats, vitamins, and other nutrients. Bile flow also facilitates the elimination of excess cholesterol, bilirubin, waste, and toxins from the body. Due to the retention of bile acids in the body, common clinical manifestations include cholestasis, pruritus, and jaundice. Off-label use of ursodeoxycholic acid, cholestyramine, rifampin, naltrexone, and sertraline are commonly used to alleviate symptoms associated with PFIC. A small study of patients with PFIC using ursodeoxycholic acid demonstrated improvements in liver function, hepatosplenomegaly, and pruritus for the majority of the group. European guidelines even discuss the use of ursodeoxycholic acid in this group of conditions. If pruritus is not relieved by ursodeoxycholic acid, then cholestyramine can be used to deplete the bile acid pool. Rifampin works by increasing the metabolism and excretion of pruritogens. Studies suggest that sertraline and naltrexone are also viable options for therapy in these patients. In addition to Bylvay, the Food and Drug Administration (FDA) approved a second ileal bile acid transporter (IBAT) inhibitor, maralixibat (Livmarli), for the treatment of this condition. After the exhaustion of pharmacologic agents, surgical procedures to interrupt the circulation of bile acids are often successful.

Alagille syndrome is an autosomal dominant liver disease which affects the bile acid transporters leading to chronic cholestasis and elevations of serum bile acids. This condition is identified by the presence of a mutation or deletion of the *JAG1* gene or *NOTCH2* gene. Clinical manifestations include cholestasis, pruritus, xanthomas, and jaundice. Progression of the disease can lead to fibrosis and cirrhosis. Although the complete mechanism by which Bylvay improves pruritus in both PFIC and ALGS patients is unknown, it may involve inhibition of the ileal bile acid transporter, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids. Currently, Bylvay and Livmarli are the only FDA approved medications for this condition. Other drug therapies, such as ursodiol, rifampin, and cholestyramine have been used off label for decades to treat pruritus. Ursodiol has demonstrated the ability to decrease the advancement of liver fibrosis in related cholestatic conditions. Given the historical use of ursodiol, rifampin, and cholestyramine for cholestatic pruritus and Bylvay's primary outcome measurement of itch scores (and not outcomes data), it is reasonably appropriate to recommend a trial of off-label, yet clinically accepted, alternative medications.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Bylvay was approved in 2021 for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis. In June of 2023, Bylvay was approved for the treatment of cholestatic pruritus in patients 12 months of age and older with Alagille syndrome.

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 federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Bylvay in PFIC was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial (Trial 1). Trial 1 included 62 pediatric patients, aged 6 months to 17 years, with a confirmed molecular diagnosis of progressive familial intrahepatic cholestasis (PFIC) type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the *ABCB11* gene that predict non-function or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in the trial. Patients were randomized to placebo (n=20), 40 mcg/kg (n=23), or 120 mcg/kg (n=19) of Bylvay. Bylvay was administered once daily with a meal in the morning. In patients weighing less than 19.5 kg or patients who could not swallow the whole capsule, study drug was sprinkled on soft food and then administered orally. Of the 62 patients, 27% had PFIC type 1, and 73% had PFIC type 2. The mean (standard error [SE]) scratching score in the 2 weeks prior to baseline was 2.9 (0.08). Baseline mean (SE) eGFR was 164 (30.6) mL/min/1.73 m^2. Baseline median (range) ALT, AST, and total bilirubin were 65 (16-798) U/L, 83.5 (32-405) U/L, and 2.2 (0.2-18.6) mg/dL, respectively. In Trial 1, a total of 13 patients discontinued prematurely either due to no improvement in pruritus (n=11) or due to adverse reactions (n=2); 5/20 (25%) patients discontinued from the placebo arm and 8/42 (19%) patients discontinued from the Bylvay arms. A total of 11 of the 13 patients rolled over to a second trial, Trial 2, to receive Bylvay 120 mcg/kg/day. One patient treated with Bylvay 120 mcg/kg/day withdrew from the trial due to a treatment-emergent adverse event of diarrhea.

Given the patients' young age, a single-item observer-reported outcome (ObsRO) was used to measure patients' scratching as observed by their caregiver twice daily (once in the morning and once in the evening). Scratching was assessed on a 5-point ordinal response scale, with scores

ranging from 0 (no scratching) to 4 (worst possible scratching). Patients treated with Bylvay demonstrated greater improvement in pruritus compared with placebo. The Bylvay groups had 30.1% to 35.4% (depending on the dose) of assessments scored as 0 or 1 compared to 13.2% of the placebo group.

The efficacy of Bylvay in ALGS was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial (Trial 3). Trial 3 was conducted in 52 pediatric patients, aged 6 months to 15 years, with a confirmed diagnosis of ALGS and presence of pruritus at baseline. Patients who had decompensated liver disease, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT was greater than 10-times the upper limit of normal (ULN) at screening, whose total bilirubin was greater than 15-times the ULN at screening, or who had received a liver transplant were excluded from Trial 3. Patients were randomized to receive placebo (n=17) or Bylvay 120 mcg/kg (n=35). The study drug was administered once daily with a meal in the morning. In patients weighing less than 19.5 kg or patients who could not swallow the whole capsule, the study drug was sprinkled on soft food and then administered orally. Of the 52 patients, 92% of patients had the *JAG1* mutation and 8% had the *NOTCH2* mutation. The mean (standard deviation [SD]) scratching score in the 2 weeks prior to baseline was 2.9 (0.6). Baseline mean (SD) eGFR was 159 (51.4) mL/min/1.73 m^2. Baseline median (range) ALT, AST, and total bilirubin were 152 (39-403) U/L, 135 (57-427) U/L, and 2.0 (0.4-11.4) mg/dL, respectively.

The same 5-point ordinal scratching scale used in Trials 1 & 2 was also used in Trial 3. Scratching scores were observed and reported by the patients' caregiver twice daily (once in the morning and once in the evening). The study was designed to compare the change in average scratching score from baseline to month 6 in patients receiving Bylvay vs. placebo. At Month 6, a statistically significant greater change in average scratching score was seen in patients receiving Bylvay compared to patients who received placebo (-1.7 vs -0.8; $P<0.002$). Patients treated with Bylvay demonstrated greater improvement in pruritus compared with placebo.

References

1. Bylvay [package insert]. Albireo Pharma, Inc. Boston, Massachusetts. Updated January 2024.
2. Bylvay Drug Evaluation. Express Scripts. Updated August 2021.
3. Inherited Disorders Associated With Conjugated Hyperbilirubinemia. UpToDate. Accessed March 2022.
4. www.clinicaltrials.gov. NCT03566238. Accessed March 2022.

Policy History

Original Effective Date: 05/09/2022
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04/07/2022 Medical Policy Committee review
04/13/2022 Medical Policy Implementation Committee approval. New policy.

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04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. Added a new FDA approved indication for ALGS, included relevant criteria and background information.
04/03/2025	Medical Policy Committee review
04/09/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2026

*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.