PHARMACY COVERAGE GUIDELINE

BYLVAY™ (odevixibat)
LIVMARLI™ (maralixibat)
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:** Bylvay (odevixibat), Livmarli (maralixibat), 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 Gastroenterologist or Hepatologist

2. Request is **ONE** of the following:
    a. **For Bylvay (odevixibat) ONE** of the following:
        i. Individual is 12 months of age or older with a confirmed diagnosis of cholestatic pruritus from Alagille Syndrome (ALGS)

ii. Individual is 3 months of age or older with a confirmed diagnosis of pruritus from Progressive Familial Intrahepatic Cholestasis (PFIC) types 1 & 2

b. **For Livmarli (maralixibat) ONE** of the following:
   i. Individual is 3 months of age or older with a confirmed diagnosis of cholestatic pruritus from Alagille Syndrome (ALGS)
   ii. Individual is 12 months of age or older with a confirmed diagnosis of cholestatic pruritus from Progressive Familial Intrahepatic Cholestasis (PFIC) types 1, 2, 3, 4, & 6

3. Individual's diagnosis is confirmed by **ONE** of the following:
   a. **For Alagille Syndrome (ALGS)**, confirmed by **ONE** of the following:
      i. Presence of *JAG1(*or *JAGGED1)* or *NOTCH2* gene mutation
      ii. Clinical confirmation with **BOTH** of the following:
         1. Bile duct paucity on liver biopsy
         2. Meets three or more major clinical features of ALGS (see Definitions section)

   b. **For Progressive familial intrahepatic cholestasis (PFIC)**, confirmed by **ONE** of the following:
      i. Presence of biallelic pathogenic gene mutations (e.g., *ATP8B1* gene*, ABCB11* gene*, ABCB4* gene*, TJP2* gene*,* and *MYO5B* gene)
      ii. Clinical signs and symptoms of PFIC

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. Liver tests (e.g., ALT [alanine aminotransferase], AST [aspartate aminotransferase], TB [total bilirubin]), DB [direct bilirubin] and International Normalized Ratio [INR]
   b. Fat-soluble vitamins (A, D, E, and K), supplement if deficiency is observed
   c. Serum bile acids are above the upper limit of normal
   d. Individual is experiencing at least moderate pruritus as determined by an average pruritus score of at least two or more using the itch reported outcome instrument (see Definitions section)

5. There is evidence of cholestasis with **ONE** or more of the following:
   a. Fasting total serum bile acid greater than three times the upper limit of normal (ULN) for age
   b. Direct bilirubin is greater than 1 mg/dL
   c. Individual has fat soluble vitamin deficiency that is otherwise unexplainable
   d. Gamma glutamyl transpeptidase (GGT) greater than three times the ULN for age
   e. Individual has intractable pruritus explainable only by liver disease

6. **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)

7. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for at least **TWO** of the following systemic medications for pruritus from ALGS or PFIC:
   a. Cholestyramine
   b. Naltrexone
   c. Phenobarbital

d. Rifampin
e. Sertraline
f. Ursodeoxycholic acid (ursodiol)

8. Individual does not have **ANY** of the following:
   a. Hepatic decompensation such as variceal hemorrhage, ascites, hepatic encephalopathy
   b. Clinically significant portal hypertension
   c. Past medical history or ongoing chronic cirrhosis
   d. Decompensated cirrhosis
   e. Past medical history or ongoing presence of other types of liver disease
   f. Surgical history of disruption of enterohepatic circulation (biliary diversion surgery) within the previous 6-months
   g. Liver transplantation or a liver transplantation that is planned for within the next 6-months
   h. Uncontrolled, recalcitrant pruritic condition other than from PFIC or ALGS
   i. PFIC type 2 individuals with specific *ABC11* gene variant that results in a non-functioning or complete absence of bile salt export pump protein (BSEP-3)

9. Bylvay and Livmarli will not be used in combination with each other

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Bylvay (odevixibat), Livmarli (maralixibat), 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 Gastroenterologist or Hepatologist

2. Individual's age is consistent per product label for diagnosis and medication

3. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
   a. Achieved and maintains at least a 1-point reduction in the average daily Itch Reported Outcome (ItchRO) over baseline
   b. No evidence of itching rated by the individual or caregiver as very itchy or very, very itchy (extremely itchy)
   c. Achieved and maintains a decrease in serum bile acids

4. Individual has been adherent with the medication

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. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:

a. Persistent or recurrent liver test abnormalities in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, and International Normalized Ratio
b. Persistent diarrhea, abdominal pain, vomiting with no alternative etiology identified
c. Persistent or worsening fat-soluble vitamin deficiency despite supplementation
d. Hepatic decompensation event such as variceal hemorrhage, ascites, hepatic encephalopathy
e. **Additional for Livmarli only:** Individual less than 5 years of age with suspected propylene glycol toxicity (hemolysis, hyperosmolarity with anion gap metabolic acidosis, acute kidney injury, and CNS toxicity)

7. Individual does not have **ANY** of the following:
   a. Hepatic decompensation such as variceal hemorrhage, ascites, hepatic encephalopathy
   b. Clinically significant portal hypertension
   c. Past medical history or ongoing chronic cirrhosis
   d. Decompensated cirrhosis
   e. Past medical history or ongoing presence of other types of liver disease
   f. Surgical history of disruption of enterohepatic circulation (biliary diversion surgery) within the previous 6-months
   g. Liver transplantation or a liver transplantation that is planned for within the next 6-months
   h. Uncontrolled, recalcitrant pruritic condition other than from PFIC or ALGS
   i. PFIC type 2 individuals with specific ABC11 gene variant that results in a non-functioning or complete absence of bile salt export pump protein (BSEP-3)
   j. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation

8. Bylvay and Livmarli will not be used in combination with each other

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:

Livmarli (maralixibat) is a reversible inhibitor of the ileal bile acid transporter (IBAT) indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) who are 3-months of age and older. It is also indicated for the treatment of cholestatic pruritus in patients 12 months of age and older with progressive familial intrahepatic cholestasis (PFIC). Livmarli (maralixibat) is not recommended in a subgroup of PFIC type 2 patients with specific *ABCB11* variants resulting in non-functional or complete absence of bile salt export pump (BSEP) protein. Livmarli (maralixibat) decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum. Although the complete mechanism by which maralixibat improves pruritus in ALGS and PFIC patients is

unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids.

Bylvay (odevixibat) is a reversible inhibitor of IBAT, is 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 with ALGS in patients 12-months of age and older. Bylvay (odevixibat) may not be effective in PFIC type 2 patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3). Odevixibat decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum. Although the complete mechanism by which odevixibat improves pruritus in patients is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, observed by a decrease in serum bile acids.

ALGS is characterized by chronic cholestasis with lack of the interlobular bile ducts on liver biopsy. Associated features seen in most patients include cardiac anomalies, butterfly vertebrae, posterior embryotoxon of the eye, and characteristic facial features.

ALGS is an autosomal dominant inherited condition. The syndrome is also known as syndromic lack of the interlobular bile ducts or arteriohepatic dysplasia. The clinical diagnosis of ALGS in an infant with cholestasis includes the characteristic clinical features and a liver biopsy demonstrating reduced number of the interlobular bile ducts. In patients with clinical characteristics suggestive of ALGS, the diagnosis can also be made or confirmed by the finding of a *JAG1(*or *JAGGED1)* or *NOTCH2* gene mutation.

Medical management of patients with ALGS depends on establishing the diagnosis and treating each affected organ system. Pruritus is a common symptom in patients with ALGS. It occurs in over 60% of patients. The pathophysiology of pruritus in patients with ALGS is not completely understood. Cholestasis is seen with many hepatobiliary disorders. One difficult symptom associated with cholestasis is pruritus, which can range in severity from mild to extreme.

Pruritus may be treated with ursodeoxycholic acid (ursodiol), rifampin, bile acid sequestrants (such as cholestyramine, colesevelam), naltrexone, sertraline, and intestinal bile acid transport (IBAT) inhibitors.

Initial studies of the IBAT inhibitor maralixibat have shown some benefit. Pruritus was assessed using Itch Reported Outcome (ItchRO[Obs]) measure, using an electronic diary (eDiary) completed by the patient or caregiver twice daily (morning and evening). ItchRO(Obs) score ranges from 0 to 4, with the higher score indicating increasing itch severity. The highest score between the morning and evening ItchRO(Obs) reports represented the daily score: a measure of the worst itching over the previous 24-hour period.

Approximately 40% of the patients with ALGS and pruritus, the pruritus is refractory to medical treatment. In these cases, biliary diversion or liver transplantation may be indicated.

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of disorders caused by homozygous or compound heterozygous variants and is characterized by defective secretion of bile acids or other components of bile. It presents in infancy or childhood and is associated with growth failure and progressive liver disease.

There are several types of PFIC involving several gene mutations. PFIC1 is caused by variants in the aminophospholipid flippase (*ATP8B1*) gene, which encodes the familial intrahepatic cholestasis 1 (FIC1) protein, while PFIC2 results from variants in the *ABCB11* gene, which encodes the bile salt export pump (BSEP) protein. PFIC2 is further categorized into BSEP subgroups based on specific variants. The BSEP-1 subgroup includes patients with at least one p.D482G (c.1445A>G) or p.E297G (c.890A>G) variant, BSEP-2 includes patients with at least one missense variant other than p.D482G or p.E297G (non BSEP-1), and BSEP-3 includes patients with variants that are predicted to encode a non-functional protein. PFIC3 is caused by variants in the *ABCB4* gene, which encodes multidrug resistance protein 3 (*MDR3*). PFIC4 is caused by variants in the tight junction protein 2 gene (*TJP2*), which encodes TJP2. PFIC5 is caused by variants in *NR1H4* gene which encodes for nuclear receptor subfamily 1 group h member 4. PFIC6 is caused by variants in myosin 5B (*MYO5B*), which encodes MYO5B.

Intractable pruritus is a dominant feature of PFIC types 1 and 2 and both are associated with life-threatening cholestasis. In all forms of PFIC, use of ursodeoxycholic acid, may improve liver function in some patients, and may relieve the pruritus associated with the disorder.

Definitions:

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

Major clinical criteria/features for Alagille syndrome include:

- Liver biopsy demonstrating reduced number of the interlobular bile ducts
- Cholestasis, cardiac, renal, vascular, ocular, skeletal involvement, or characteristic “Alagille” facies

Hepatic	Chronic cholestasis, jaundice, conjugated hyperbilirubinemia, cirrhosis, pruritus, xanthomas
Cardiac	Murmur or cardiac anomalies. The most common finding is peripheral pulmonary stenosis; other anomalies include tetralogy of Fallot, ductus arteriosus, septal defects, or coarctation of the aorta
Renal	Renal involvement (19 to 74 percent). The most common finding is renal dysplasia; other disorders include glomerular mesangiolipidosis or renal tubular acidosis
Vertebral/Skeletal	Butterfly vertebrae, occasionally hemivertebrae, fusion of adjacent vertebrae, and spina bifida occulta
Facies	Dysmorphic facies, consisting of broad nasal bridge, triangular facies (broad forehead and pointed chin), and deep-set eyes
Ocular	Most commonly posterior embryotoxon (prominent Schwalbe line). Other findings may include optic disc abnormalities, hypopigmentation of the peripheral retina, pseudopapilledema, and true papilledema (associated with intracranial hypertension)
Ears	Hearing loss

Alagille facies:

- Facial features are triangular, with a prominent, broad forehead, deep-set eyes, prominent ears, a pointed chin, and a straight nose with a bulbous tip

- The facial features change over time, with a more triangular shape during childhood and prominence of the jaw as patients reach adulthood

Itch Reported Outcome (ItchRO):

- Can be completed by the patient (ItchRO[Pt]) or a caregiver/observer (ItchRO[Obs])
- It is performed in the morning and evening
- The daily score is the highest (worst) score from the morning and evening reports
- Average daily score is the sum of all daily scores divided by the number of days the ItchRO was completed

Completed by the patient (ItchRO[Pt]) in the morning and evening				
I didn't feel itchy	I felt a little bit itchy	I felt pretty itchy	I felt very itchy	I felt very, very itchy
0	1	2	3	4

Completed by caregiver/observer (ItchRO[Obs]) in the morning and evening				
Not itchy at all	A little bit itchy	Somewhat/moderately itchy	Very itchy	Extremely itchy
0	1	2	3	4

Resources:

Bylvay (odevixibat) product information, revised by Albireo Pharma, Inc. 06-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 26, 2024.

Livmarli (maralixibat) product information, revised by Mirum Pharmaceuticals, Inc. 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 11, 2024.

Kohut TJ, Loomes K. Alagille syndrome. In: UpToDate, Rand EB, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2024. Topic last updated May 10, 2024. Accessed September 26, 2024.

Poupon R, Chopra S. Pruritus associated with cholestasis. In: UpToDate, Lindor KD, Law K (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2024. Topic last updated March 03, 2023. Accessed September 26, 2024.

Roy-Chowdhury J, Roy-Chowdhury N. Inherited disorders associated with conjugated hyperbilirubinemia. In: UpToDate, Lindor KD, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2024. Topic last updated May 10, 2024. Accessed September 26, 2024.

Wehrman A, Loomes KM. Causes of cholestasis in neonates and young infants. In: UpToDate, Abrams SA, Rand EB, Hoppin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2024. Topic last updated July 25, 2023. Accessed September 26, 2024.

Shneider BL, Spino C, Kamath BM, et al.: Placebo-controlled randomized trial of an Intestinal Bile Salt Transport Inhibitor for pruritus in Alagille Syndrome. Hepatology Communications; 2018; 2(10): 1184-1198. Accessed October 22, 2021. Re-reviewed September 27, 2024.

Shneider BL, Spino C, Kamath BM, et al.: Placebo-controlled randomized trial of an Intestinal Bile Salt Transport Inhibitor for pruritus in Alagille Syndrome. Hepatology Communications; 2018; 2(10): 1184-1198_Supplemental Tables. Accessed October 12, 2023. Re-reviewed September 27, 2024.

Kamath BM, Abetz-Webb L, Kennedy C, et al.: Development of a novel tool to assess the impact of itching in pediatric cholestasis. Patient 2017 July 14; DOI 10.1007/s40271-017-0266-4. Accessed October 23, 2021. Re-reviewed September 27, 2024.

Thompson RJ, Arnell H, Artan R, et al.: Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomized, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2022; 7: 830–42. https://doi.org/10.1016/ S2468-1253 (22) 00093-0. Access June 18, 2023. Re-reviewed September 27, 2024.

Thompson RJ, Arnell H, Artan R, et al.: Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomized, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2022; 7: 830–42. Supplement. https://doi.org/10.1016/ S2468-1253 (22) 00093-0. Access June 18, 2023. Re-reviewed September 27, 2024.