BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 11/18/2021
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LIVMARLI™ (maralixibat)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

LIVMARLI™ (maralixibat)

Criteria:

- **Criteria for initial therapy:** Livmarli (maralixibat) is considered ***medically necessary*** and will be approved when **ALL** of 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. Individual is 1 years of age or older

  3. A confirmed diagnosis of moderate to severe cholestatic pruritus associated with Alagille Syndrome (ALGS) and characteristic clinical features by **ONE** of the following:
     a. Liver biopsy demonstrating reduced number of interlobular bile ducts
     b. *JAG1(*or *JAGGED1)* or *NOTCH2* gene mutation

  4. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Fat-soluble vitamins (A, D, E, and K) levels
     b. Average daily Itch Reported Outcome (ItchRO) by the patient or observer as 2 or more

  5. **For a individuals 3 years of age or older** documented failure, contraindication per FDA label, intolerance, or not a candidate for Cholestyramine

  6. Individual does not have hepatic decompensation or cirrhosis

  7. Individual does not have a surgical history of disruption of enterohepatic circulation (biliary diversion surgery) within the previous 6-months

  8. Individual does not have a liver transplantation or liver transplantation is planned for within the next 6-months

  9. Individual does not have a past medical history or ongoing presence of other types of liver disease

  10. There are no significant interacting drugs

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Livmarli (maralixibat) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  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 condition has responded/worsened while on therapy

a. Response is defined as **ALL** of the following:
   i. Achieved and maintains at least a 1-point reduction in the average daily Itch Reported Outcome (ItchRO) over baseline
   ii. No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
   a. Significant adverse effect such as:
      i. Persistent or recurrent liver test abnormalities
      ii. Persistent diarrhea, abdominal pain, vomiting with no alternative etiology identified
      iii. Persistent or worsening fat-soluble vitamin deficiency despite supplementation
      iv. Hepatic decompensation event such as variceal hemorrhage, ascites, hepatic encephalopathy

5. Individual does not have hepatic decompensation or cirrhosis

6. Individual does not have a surgical history of disruption of enterohepatic circulation (biliary diversion surgery) within the previous 6-months

7. Individual does not have a liver transplantation or liver transplantation is planned for within the next 6-months

8. Individual does not have a past medical history or ongoing presence of other types of liver disease

9. There are no significant interacting drugs

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 a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

LIVMARLI™ (maralixibat)

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) in patients 1 year of age and older. It 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 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.

ALGS is characterized by chronic cholestasis with paucity 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 paucity 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.

Pruritus may be treated with ursodeoxycholic acid (ursodiol), rifampin, or bile acid sequestrants (such as cholestyramine, colesevelam). Treatment with naltrexone has been shown to improve pruritus in children with cholestatic liver disease in several case series and one small randomized trial. 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.

Definitions:

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

LIVMARLI™ (maralixibat)

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:

Livmarli (maralixibat) product information, revised by Mirum Pharmaceuticals, Inc. 09-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 21, 2021.

Erlichman J, 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. Accessed October 22, 2021.

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.

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.