maralixibat oral solution (Livmarli™)

Policy # 00775
Original Effective Date: 03/14/2022
Current Effective Date: 12/11/2023

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 maralixibat oral solution (Livmarli)™‡ for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for maralixibat oral solution (Livmarli) will be considered when the following criteria are met:

Initial:

- Patient has a diagnosis of cholestatic pruritis due to Alagille syndrome; AND
- Alagille syndrome diagnosis has been confirmed by genetic testing demonstrating *JAG1* or *NOTCH2* deletion or mutations; AND
- Patient is at least 3 months of age or older; AND
- Patient's serum bile acid concentration is above the upper limit of normal reference range for the reporting laboratory; AND
- Patient does NOT have cirrhosis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met).*
- Patient does NOT have portal hypertension; AND
  *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met).*

- Patient does NOT have a history of a hepatic decompensation event (examples include variceal hemorrhage, ascites, hepatic encephalopathy); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met).*
- Patient has tried and failed (e.g., intolerance or inadequate response) TWO other medications for this condition (e.g., cholestyramine, rifampin, and ursodiol) 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: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

Continuation:

- Initial patient selection criteria were met; AND
- Patient does NOT have cirrhosis; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met).*
- Patient does NOT have portal hypertension; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met).*
- Patient does NOT have a history of a hepatic decompensation event (examples include variceal hemorrhage, ascites, hepatic encephalopathy); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met).*
- Patient has responded to therapy with the requested product (i.e., a decrease in serum bile acids and a decrease in pruritis).
  *(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)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of maralixibat oral solution (Livmarli) when the patient has cirrhosis, portal hypertension, or history of a hepatic decompensation event to be **not medically necessary.****

Based on review of available data, the Company considers the use of maralixibat oral solution (Livmarli) when the patient has not tried and failed (e.g., intolerance or inadequate response) TWO other medications for the requested condition (e.g., cholestyramine, rifampin, and ursodiol) to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of maralixibat oral solution (Livmarli) when the patient has not responded to therapy 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 maralixibat oral solution (Livmarli) when the patient selection criteria are not met (EXCEPT those denoted as **not medically necessary****) to be **investigational.***

Background/Overview

Livmarli is an ileal bile acid transporter (IBAT) inhibitor indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 3 months of age and older. Livmarli is supplied as an oral solution containing 9.5 mg of drug per milliliter of solution. The recommended dosage is 380 mcg/kg once daily, taken 30 minutes before the first meal of the day. Dosing should be started at 190 mcg/kg administered orally once daily; after one week, the dosage can be increased to 380 mcg/kg once daily, as tolerated. The maximum daily dose volume for patients above 70kg is 3 mL or 28.5 mg per day. Refer to the package insert for complete details on dosing. Patients with cirrhosis, portal hypertension, or history of a hepatic decompensation event were not included in clinical trials.

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, pruritis, xanthomas, and jaundice. Progression of the disease can lead to fibrosis and cirrhosis. Livmarli decreases the reabsorption of bile acids from the terminal ileum. The exact mechanism of action of Livmarli on improving pruritis is unknown however it more than likely involves its mechanism of action. Other drug therapies, such as ursodiol, rifampin, and cholestyramine have been used off label for decades to treat pruritis. 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 pruritis and Livmarli'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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Livmarli, approved in late 2021, is an ileal bile acid transporter (IBAT) inhibitor indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older. In March of 2023, the FDA label was updated to include approval for patients 3 months of age 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 federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Livmarli was assessed in Trial 1, which consisted of an 18-week open-label treatment period; a 4-week randomized, double-blind, placebo-controlled drug-withdrawal period; a subsequent 26-week open-label treatment period; and a long-term open-label extension period.

Thirty-one pediatric Alagille syndrome patients with cholestasis and pruritus were enrolled, with 90.3% of patients receiving at least one medication to treat pruritus at study entry. All patients had

a *JAG1* mutation. Patients were administered open-label treatment with Livmarli 380 mcg/kg once daily for 13 weeks after an initial 5-week dose-escalation period; two patients discontinued treatment during this first 18 weeks of open-label treatment. The 29 patients who completed the open-label treatment phase were then randomized to continue treatment with Livmarli or receive matching placebo during the 4- week drug withdrawal period at Weeks 19-22 (n=16 placebo, n=13 Livmarli). All 29 patients completed the randomized, blinded drug withdrawal period; subsequently, patients received open-label Livmarli at 380 mcg/kg once daily for an additional 26 weeks.

Given the patients' young age, a single-item observer-reported outcome was used to measure patients' pruritus symptoms as observed by their caregiver twice daily (once in the morning and once in the evening) on the Itch Reported Outcome Instrument (ItchRO[Obs]). Pruritus symptoms were assessed on a 5-point ordinal response scale, with scores ranging from 0 (none observed or reported) to 4 (very severe). Patients were included in Trial 1 if their average pruritus score was greater than 2.0 (moderate) in the 2 weeks prior to baseline. The average of the worst daily ItchRO(Obs) pruritus scores was computed for each week. For randomized patients, the mean (SD) at baseline (pre-treatment) was 3.1 (0.5) and the mean (SD) at Week 18 (pre-randomized withdrawal period) was 1.4 (0.9). On average, patients administered Livmarli for 22 weeks maintained pruritus reduction whereas those in the placebo group who were withdrawn from Livmarli after Week 18 returned to baseline pruritus scores by Week 22. After re-entering the open-label treatment phase, both randomized treatment groups had similar mean pruritus scores by Week 28, the first week placebo patients received the full dosage of Livmarli after withdrawal. These observer-rated pruritus results are supported by similar results on patient-rated pruritus in patients 5 years of age and older who were able to self-report their itching severity.

References

1. Livmarli [package insert]. Mirum Pharmaceuticals. Foster City, California. Updated March 2023.
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5. Kamath BM, Baker A, Houwen R, Todorova L, Kerkar N. Systematic review: the epidemiology, natural history, and burden of Alagille syndrome. J Pediatr Gastroenterol Nutr. 2018;67(2):148-156.
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Policy History

Original Effective Date: 03/14/2022
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02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. New policy.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. Updated criteria to reflect newest FDA label update for approval in patients 3 months of age and older.

Next Scheduled Review Date: 11/2024

*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: 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.

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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.