PRIOR AUTHORIZATION POLICY

POLICY: Hepatology – Livmarli Prior Authorization Policy
- Livmarli™ (maralixibat oral solution – Mirum)

REVIEW DATE: 10/16/2024

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Livmarli, an ileal bile acid transporter (IBAT) inhibitor, is indicated for the treatment of:[1]

- Cholestatic pruritus in patients ≥ 3 months of age with **Alagille syndrome** (ALGS).
- Cholestatic pruritus in patients ≥ 12 months of age with **progressive familial intrahepatic cholestasis** (PFIC).

Disease Overview

ALGS is a rare liver disease defined by genetic deletion or genetic pathogenic variants affecting bile acid transporters (e.g., deletion or variant of the *JAG1* gene or *NOTCH2* gene).[2-4] **PFIC** is a group of rare, autosomal recessive liver diseases defined by genetic pathogenic variants affecting bile acid transporters (e.g., variants of the *ATP8B1* gene, *ABCB11* gene, *ABCB4* gene, *TJP2* gene, *NR1H4* gene, or *MYO5B* gene).[5-7] Progression of both diseases can cause liver fibrosis, cirrhosis, or end-stage liver disease and leads to death at an early age in life (infancy to adolescence).

Cholestasis, jaundice, and pruritus are common symptoms in patients with PFIC and ALGS.[2,5] Although the complete mechanism by which Livmarli improves pruritus in these 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.[1] Cholestyramine, rifampicin, and ursodeoxycholic acid (ursodiol) have been used off-label for decades to alleviate symptoms related to PFIC and ALGS.[7-9] Cholestyramine, ursodeoxycholic acid, rifampicin, naltrexone, and sertraline are recommended in clinical practice guidelines from the European Association for the Study of the Liver (2009).

Clinical Efficacy

The efficacy of Livmarli for ALGS was evaluated in one study that included an 18-week open-label treatment period, followed by a 4-week randomized, double-blind, placebo-controlled drug withdrawal period.[1] The study was conducted in 31 pediatric patients with ALGS (1 year to 15 years of age) with cholestasis and pruritus. All enrolled patients had a *JAG1* genetic variant, elevated serum bile acid concentration, and presence of at least moderate pruritus at baseline. Approximately 90.3% of patients were receiving at least one medication to treat pruritus at study entry. Patients treated with Livmarli demonstrated greater improvement in pruritus compared to placebo. Safety and tolerability in infants less than 1 year of age was assessed in a 13-week, open label, phase II study of 12 patients. Livmarli was well-tolerated with treatment emergent adverse events, which were mostly Grade 1 and unrelated to therapy.

The efficacy of Livmarli for PFIC was evaluated in one 26-week, randomized, placebo-controlled pivotal trial.[1] Efficacy was evaluated in 64 patients (12 months to 17 years of age) with a clinical genetic confirmation of PFIC. Patients had to have an elevated serum bile acid concentration along with presence of moderate to severe pruritus at baseline. Most patients were on stable ursodeoxycholic acid (89.1%) or rifampicin (51.6%) therapy at baseline. Patients treated with Livmarli demonstrated greater improvement in pruritus compared with placebo.

Safety

Livmarli was not evaluated in patients with decompensated cirrhosis.[1] Monitor for liver test abnormalities; permanently discontinue Livmarli if a patient progresses to portal hypertension or experiences a hepatic decompensation event (e.g., variceal hemorrhage, ascites, hepatic encephalopathy).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Livmarli. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Livmarli as well as the monitoring required for adverse events and long-term efficacy, approval requires Livmarli to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Livmarli™ (maralixibat oral solution (Mirum)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Alagille Syndrome**. Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi and vii):
     - **i.** Patient is ≥ 3 months of age; AND
     - **ii.** Patient has moderate-to-severe pruritus, according to the prescriber; AND
     - **iii.** Diagnosis of Alagille syndrome was confirmed by genetic testing demonstrating a *JAG1* or *NOTCH2* deletion or pathogenic variant; AND
     - **iv.** Patient has a serum bile acid concentration above the upper limit of the normal reference range for the reporting laboratory; AND
     - **v.** Patient has tried at least two systemic medications for Alagille syndrome, unless contraindicated; AND
       Note: Systemic medications for Alagille syndrome include cholestyramine, naltrexone, rifampicin, sertraline, and ursodeoxycholic acid (ursodiol).
     - **vi.** Patient does not have any of the following (a, b, or c):
       - **a)** Cirrhosis; OR
       - **b)** Portal hypertension; OR
       - **c)** History of a hepatic decompensation event; AND
         Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.
     - **vii.** The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in Alagille syndrome.
   - **B)** Patient is Currently Receiving Livmarli. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient does not have any of the following (a, b, or c):
       - **a)** Cirrhosis; OR
       - **b)** Portal hypertension; OR
       - **c)** History of a hepatic decompensation event; AND
         Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.
     - **ii.** Patient had response to therapy, as determined by the prescriber; AND
       Note: Examples of response to therapy include decrease in serum bile acids and decrease in pruritus.
     - **iii.** The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in Alagille syndrome.

2. **Progressive Familial Intrahepatic Cholestasis**. Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, v, vi and vii):

i. Patient is ≥ 12 months of age; AND
ii. Patient has moderate-to-severe pruritus, according to the prescriber; AND
iii. Diagnosis of progressive familial intrahepatic cholestasis was confirmed by genetic testing demonstrating a pathogenic gene variant affiliated with progressive familial intrahepatic cholestasis; AND
Note: Gene variants affiliated with progressive familial intrahepatic cholestasis include the *ATP8B1* gene*, ABCB11* gene*, ABCB4* gene*, TJP2* gene*, NR1H4* gene*,* and *MYO5B* gene.
iv. Patient has a serum bile acid concentration above the upper limit of the normal reference range for the reporting laboratory; AND
v. Patient has tried at least two systemic medications for progressive familial intrahepatic cholestasis, unless contraindicated; AND
Note: Systemic medications for progressive familial intrahepatic cholestasis include cholestyramine, naltrexone, rifampicin, sertraline, and ursodeoxycholic acid (ursodiol).
vi. Patient does not have any of the following (a, b, or c):
a) Cirrhosis; OR
b) Portal hypertension; OR
c) History of a hepatic decompensation event; AND
Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.
vii. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in progressive familial intrahepatic cholestasis.

B) Patient is Currently Receiving Livmarli. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
i. Patient does not have any of the following (a, b, or c):
a) Cirrhosis; OR
b) Portal hypertension; OR
c) History of a hepatic decompensation event; AND
Note: Examples of a hepatic decompensation event include variceal hemorrhage, ascites, and hepatic encephalopathy.
ii. Patient had response to therapy, as determined by the prescriber; AND
Note: Examples of response to therapy include decrease in serum bile acids and decrease in pruritus.
iii. The medication is prescribed by or in consultation with a hepatologist, gastroenterologist, or a physician who specializes in progressive familial intrahepatic cholestasis.

CONDITIONS NOT COVERED

- **Livmarli™ (maralixibat oral solution (Mirum)**

is(are) considered experimental, investigational or unproven for ANY other use(s) including the following; criteria will be updated as new published data are available.

REFERENCES

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10. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol*. 2009 Aug;51(2):237-67.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	10/18/2023
Selected Revision	**Progressive Familial Intrahepatic Cholestasis:** This condition and criteria for approval were added to the policy.	03/27/2024
Selected Revision	**Alagille Syndrome**: For diagnosis by genetic testing, the term "mutation" was rephrased to "pathogenic variant". **Progressive Familial Intrahepatic Cholestasis:** For diagnosis by genetic testing, the term "mutation" was rephrased to "pathogenic variant". Additionally, the criterion for age was changed from ≥ 5 years to ≥ 12 months of age to align with FDA indication expansion for age.	07/31/2024
Annual Revision	No criteria changes.	10/16/2024