Effective Date **7/15/2025**
Coverage Policy Number **IP0341**

Maralixibat

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Related Coverage Resources

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 where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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.

Overview

This policy supports medical necessity review for **Livmarli**™ (maralixibat) oral solution, and oral tablets.

Medical Necessity Criteria

Documentation: Documentation is required where noted in the criteria as [documentation required]. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Maralixibat (Livmarli) is considered medically necessary when the following are met:

1. **Alagille Syndrome**. Individual meets **ALL** of the following criteria:
   - **A)** 3 months of age or older
   - **B)** Has moderate-to-severe pruritus
   - **C)** Alagille syndrome confirmed by genetic testing demonstrating a *JAG1* or *NOTCH2* deletion or pathogenic variant **[documentation required]**
   - **D)** Has a serum bile acid concentration above the upper limit of the normal reference range for the reporting laboratory
   - **E)** Does not have any of the following:
     - **i.** Cirrhosis
     - **ii.** Portal hypertension
     - **iii.** History of a hepatic decompensation event (for example, variceal hemorrhage, ascites, hepatic encephalopathy)
   - **F)** Medication is being prescribed by, or in consultation with, a hepatologist, gastroenterologist, or a physician who specializes in Alagille syndrome
   - **G)** Documented failure, contraindication, or intolerance to **TWO** systemic medications for Alagille syndrome (for example, cholestyramine, rifampicin, ursodeoxycholic acid [ursodiol])

2. **Progressive Familial Intrahepatic Cholestasis**. Approve for the duration noted if the patient meets the following criteria:
   - **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.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Continuation of maralixibat (Livmarli) is considered medically necessary for Alagille Syndrome or Progressive Familial Intrahepatic Cholestasis when the above medical necessity criteria are met AND there is documentation of beneficial response (examples of response to therapy include decrease in serum bile acids and decrease in pruritus).

Authorization Duration

Initial approval duration: up to 6 months.
Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven.

Background

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).

References

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4. Treatment for Alagille syndrome. National Institute of Diabetes and Digestive and Kidney Diseases. US Department of Health and Human Services. Updated January 2019. Available at: https://www.niddk.nih.gov/health-information/liver-disease/alagille-syndrome/treatment. Accessed on October 07, 2024.
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6. Amirneni S, Haep N, Gad MA, et al. Molecular overview of progressive familial intrahepatic cholestasis. *World J Gastroenterol*. 2020 Dec 21;26(47):7470-7484.
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8. van der Woerd WL, Houwen RH, van de Graaf SF. Current and future therapies for inherited cholestatic liver diseases. *World J Gastroenterol*. 2017 Feb 7;23(5):763-775.
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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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	1/1/2025
Selected Revision	Added oral tablets to coverage policy. **Progressive Familial Intrahepatic Cholestasis:** The criterion for age was changed from ≥ 12 years to ≥ 12 months of age to align with FDA indication expansion for age. Added oral tablets to coverage policy. Added “documentation required” as noted in criteria.	7/15/2025

The policy effective date is in force until updated or retired.