Effective Date.....**11/1/2024**
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. 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.

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

Medical Necessity Criteria

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. Documented diagnosis of Alagille syndrome was confirmed by genetic testing demonstrating a *JAG1* or *NOTCH2* deletion or pathogenic variant
    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 years 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.

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 cholestatic pruritus in patients ≥ 3 months of age with **Alagille syndrome**.*[1]

Disease Overview

Alagille syndrome is a rare liver disease defined by genetic deletion or mutation affecting bile acid transporters (e.g., deletion or mutation of the *JAG1* gene or *NOTCH2* gene).[2-4] Main clinical manifestations include cholestasis, pruritus, and jaundice. Progression of the disease can cause liver fibrosis, cirrhosis, or end-stage liver disease and leads to death at an early age in life (infancy to adolescence). Pruritus is a common symptom in patients with Alagille syndrome and the pathophysiology of pruritus in these patients is not completely understood.[1] Although the complete mechanism by which Livmarli improves pruritus in patients with Alagille syndrome 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. Cholestyramine, rifampicin, and ursodeoxycholic acid (ursodiol) have been used off-label for decades to alleviate symptoms related to Alagille syndrome.[2-5]

Clinical Efficacy

The efficacy of Livmarli was evaluated in one study that involved an 18-week open-label treatment period, followed by a 4-week randomized, double-blind, placebo-controlled drug withdrawal period. The study was conducted in 31 pediatric patients with Alagille syndrome (1 year to 15 years of age) with cholestasis and pruritus. Patients enrolled all had *JAG1* mutation, elevated serum bile acid concentration, and presence of at least moderate pruritus at baseline. Patients treated with Livmarli demonstrated greater improvement in pruritus compared with placebo. Safety and tolerability in infants less than 1 year of age was assessed in a 13-week, open label, phase 2 study of 12 patients. Livmarli was well tolerated with treatment emergent adverse events, which were mostly Grade 1 and unrelated to therapy. [1]

Safety

Livmarli was not evaluated in patients with 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

1. Livmarli™ oral solution [prescribing information]. Foster City, CA: Mirum; March 2023.
2. Alagille syndrome. National Organization for Rare Disorders. Updated 2023. Available at: https://rarediseases.org/rare-diseases/alagille-syndrome/. Accessed on October 10, 2023.
3. Alagille syndrome. US National Library of Medicine. Available at: https://medlineplus.gov/genetics/condition/alagille-syndrome. Accessed on October 10, 2023.
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 10, 2023.
5. 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.