PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 10/16/2024

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Livmarli is recommended in those who meet one of the following criteria:

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) 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 RECOMMENDED FOR APPROVAL

Coverage of Livmarli is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Livmarli™ oral solution [prescribing information]. Foster City, CA: Mirum; July 2024.
2. Alagille syndrome. National Organization for Rare Disorders. Updated 2023. Available at: https://rarediseases.org/rare-diseases/alagille-syndrome/. Accessed on October 07, 2024.
3. Alagille syndrome. US National Library of Medicine. Available at: https://medlineplus.gov/genetics/condition/alagille-syndrome. Accessed on March 20, 2024.
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.
5. Davit-Spraul, A, Gonzales, E, Baussan, C, et al. Progressive familial intrahepatic cholestasis. *Orphanet J Rare Dis*. 2009;4:1.
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.
7. Gunaydin M, Bozkurter Cil AT. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. *Hepat Med*. 2018 Sep 10;10:95-104.
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.
9. Diaz-Frias J, Kondamudi NP. Alagille Syndrome. [Updated 2022 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507827/. Accessed on October 07, 2024.
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.