VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 10/19/2022; selected revision 03/29/2023

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).

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 the following criteria:

FDA-Approved Indication

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 prescriber; AND
     - **iii.** Diagnosis of Alagille syndrome was confirmed by genetic testing demonstrating a *JAG1* or *NOTCH2* deletion or mutation; 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, rifampicin, 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.

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; March 2023.
2. Alagille syndrome. National Organization for Rare Disorders. Updated 2020. Available at: https://rarediseases.org/rare-diseases/alagille-syndrome/. Accessed on October 5, 2022.

3. Alagille syndrome. US National Library of Medicine. Available at: https://medlineplus.gov/genetics/condition/alagille-syndrome. Accessed on October 5, 2022.
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 5, 2022.
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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/01/2021
Selected Revision	**Alagille Syndrome:** A *NOTCH2* gene deletion or mutation was added as an option for genetic testing.	10/20/2021
Selected Revision	**Alagille Syndrome:** The requirement for a trial of one systemic medication for Alagille syndrome was changed to require two systemic medications.	12/15/2021
Annual Revision	No criteria changes.	10/19/2022
Selected Revision	**Alagille Syndrome:** The criterion for age was changed from ≥ 1 year to ≥ 3 months of age to align with FDA indication expansion for age.	03/29/2023