Clinical Policy: Maralixibat (Livmarli)

Reference Number: PA.CP.PHAR.543
Effective Date: 08/2022
Last Review Date: 04/2023

Revision Log

Description
Maralixibat (Livmarli™) is an ileal bile acid transporter inhibitor.

FDA Approved Indication(s)
Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 3 months of age and older.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Livmarli is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Alagille Syndrome (must meet all)**:**

1. Diagnosis of ALGS-associated pruritus confirmed by one of the following (a or b):
   a. Genetic confirmation with presence of a mutation in *JAG1* or *NOTCH2*;
   b. Clinical confirmation of both of the following (i and ii):
      i. Bile duct paucity on liver biopsy;
      ii. Criteria meeting ≥ 3 of the 5 major criteria (*see Appendix D*);
2. Prescribed by or in consultation with hepatologist or gastroenterologist;
3. Age ≥ 3 months and ≤ 18 years at therapy initiation;
4. Pruritus requiring at least moderate scratching (e.g., ≥ 2 on 0-4 scale);
5. Evidence of cholestasis that is met by ≥ 1 of the following (a – e):
   a. Total serum bile acid > 3 times upper limit of normal (ULN) for age;
   b. Conjugated bilirubin > 1 mg/dL;
   c. Fat-soluble vitamin deficiency otherwise unexplainable;
   d. Gamma-glutamyl transferase > 3 times ULN for age;
   e. Intractable pruritus explainable only by liver disease;
6. Failure of ursodeoxycholic acid, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for ursodeoxycholic acid*
7. Failure of an agent used for symptomatic relief of pruritus (e.g., antihistamine, rifampin, cholestyramine), unless clinically significant adverse effects are experienced or all are contraindicated;
8. Documentation of member's current body weight in kilograms;
9. Dose does not exceed 380 mcg/kg per day, up to a maximum of 28.5 mg (3 mL) per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Alagille Syndrome (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy as evidenced by an improvement in pruritus;
3. Documentation of member's current body weight in kilograms;
4. If request is for a dose increase, new dose does not exceed 380 mcg/kg per day, up to a maximum of 28.5 mg (3 mL) per day**.**

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
   Approval duration: Duration of request or 6 months (whichever is less);
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
ALGS: Alagille syndrome
FDA: Food and Drug Administration
ULN: upper limit of normal

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ursodeoxycholic acid (Ursodiol®)*	10-30 mg/kg/day PO	N/A
rifampin (Rifadin®)	10 mg/kg PO	10 mg/kg/day
cholestyramine	4-16 g/day PO in 2 divided doses	16 g/day
antihistamine	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

**Off-label*

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: Classic Criteria, Based on Five Body Systems, for a Diagnosis of ALGS

Classic Criteria	Description
Liver/cholestasis	Usually presenting as jaundice with conjugated hyperbilirubinaemia in the neonatal period, often with pale stools
Dysmorphic facies	Broad forehead, deep-set eyes, sometimes with upslanting palpebral fissures, prominent ears, straight nose with bulbous tip, and pointed chin giving the face a somewhat triangular appearance
Heart disease	Most frequently peripheral pulmonary artery stenosis, but also pulmonary atresia, atrial septal defect, ventricular septal defect, and Tetralogy of Fallot
Axial skeleton/vertebral anomalies	Characteristic 'butterfly' vertebrae may be seen on an antero-posterior radiograph, and occasionally hemivertebrae, fusion of adjacent vertebrae, and spina bifida occulta
Eye/posterior embryotoxin	Anterior chamber defects, most commonly posterior embryotoxon, which is prominence of Schwalbe's ring at the junction of the iris and cornea

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>ALGS</td><td>Starting dose: 190 mcg/kg/day
Maintenance: 380 mcg/kg/day

<table>
<tr><th colspan="5">Individual dose volume by patient weight</th></tr>
<tr><th rowspan="2">Patient Weight (kg)</th><th colspan="2">Days 1-7 (190 mcg/kg QD)</th><th colspan="2">Beginning Day 8 (380 mcg/kg QD)</th></tr>
<tr><th>Volume QD (mL)</th><th>Dosing dispenser size (mL)</th><th>Volume QD (mL)</th><th>Dosing dispenser size (mL)</th></tr>
<tr><td>5-6</td><td>0.1</td><td rowspan="8">0.5</td><td>0.2</td><td rowspan="3">0.5</td></tr>
<tr><td>7-9</td><td>0.15</td><td>0.3</td></tr>
<tr><td>10-12</td><td>0.2</td><td>0.45</td></tr>
<tr><td>13-15</td><td>0.3</td><td>0.6</td><td rowspan="4">1</td></tr>
<tr><td>16-19</td><td>0.35</td><td>0.7</td></tr>
<tr><td>20-24</td><td>0.45</td><td>0.9</td></tr>
<tr><td>25-29</td><td>0.5</td><td>1</td></tr>
<tr><td>30-34</td><td>0.6</td><td rowspan="4">1</td><td>1.25</td><td rowspan="4">3</td></tr>
<tr><td>35-39</td><td>0.7</td><td>1.5</td></tr>
<tr><td>40-49</td><td>0.9</td><td>1.75</td></tr>
<tr><td>50-59</td><td>1</td><td>2.25</td></tr>
<tr><td>60-69</td><td>1.25</td><td>3</td><td>2.5</td></tr>
</table>
</td><td>380 mcg/kg/day, up to a maximum of 28.5 mg/day (3 mL/day)</td></tr>
</table>

Indication	Dosing Regimen					Maximum Dose
	70 or higher	1.5		3		

VI. Product Availability

Oral solution: 9.5 mg/mL (30 mL bottle)

VII. References

1. Livmarli Prescribing Information. Foster City, CA: Mirum Pharmaceuticals, Inc.; March 2023. Available at: https://files.mirumpharma.com/livmarli/livmarli-prescribinginformation.pdf. Accessed April 5, 2023.
2. Safety and efficacy study of LUM001 with a drug withdrawal period in participants with Alagille Syndrome (ALGS) (ICONIC). ClinicalTrials.gov Identifier: NCT02160782. Available at: https://clinicaltrials.gov/ct2/show/NCT02160782. Accessed May 4, 2022.
3. Kamath BM, Baker A, Houwen R, et al. Systematic review: the epidemiology, natural history, and burden of Alagille Syndrome. J Pediatr Gastroenterol Nutr 2018 Aug;67(2):148-156.
4. Turnpenny PD and Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2012 Mar; 20(3): 251–257.
5. Gonzales E, Hardikar W, Stormon M, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. Lancet. 2021 Oct 30; 398(10311): 1581-1592.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	07/2022	
RT4: updated FDA-approved indication for pediatric extension from 1 year to 3 months of age and older.	04/2023	