Clinical Policy: Maralixibat (Livmarli)

Reference Number: PA.CP.PHAR.543
Effective Date: 08/2022
Last Review Date: 04/20234

Revision Log

Description

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

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

Progressive familial intrahepatic cholestasis (PFIC) 5 years of age and older
Limitation(s) of use: Livmarli is not recommended in a subgroup of PFIC type 2 with specific ABCB11 variants resulting in non-functional or complete absence of bile salt export pump (BSEP) protein.

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 classic 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, see *Appendix E*);
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. Progressive Familial Intrahepatic Cholestasis (must meet all)**:**

1. Diagnosis of genetically confirmed PFIC (formerly known as Byler disease or syndrome) with presence of both of the following (a and b);
    1. Has moderate to severe pruritis (e.g., ≥ 2 on 0 to 4 scale);
    2. Serum bile acid (sBA) levels > 3 times the upper limit of normal (ULN) for age;
2. Prescribed by or in consultation with a hepatologist or gastroenterologist;
3. Age ≥ 5 years;
4. For PFIC type 2, member does not have ABCB11 gene variants resulting in non-functional or complete absence of the BSEP protein;
5. Failure of ursodeoxycholic acid, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for ursodeoxycholic acid*
6. 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;
7. Livmarli is not prescribed concurrently with other IBAT inhibitors (e.g., Bylvay™);
8. Documentation of member's current body weight in kg;
9. Dose does not exceed 1,140 mcg/kg per day, up to a maximum of 38 mg (4 mL) per day.

Approval duration: 6 months

C. 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. Progressive Familial Intrahepatic Cholestasis (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, including but not limited to, improvement in any of the following parameters:
   a. Improvement in pruritis;
   b. Reduction of sBA from baseline;
3. Documentation of member's current body weight in kg;
4. If request is for a dose increase, new dose does not exceed 1,140 mcg/kg per day, up to a maximum of 38 mg (4 mL) per day.

Approval duration: 12 months

C. 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
BSEP: bile salt export pump
FDA: Food and Drug Administration
IBAT: ileal bile acid transporter
ItchRO: itch reported outcome
PFIC: progressive familial intrahepatic cholestasis
sBA: serum bile acid
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 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

- Contraindication(s): patients with prior or active hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy)
- Boxed warning(s): 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

Appendix E: Itch Reported Outcome (ItchRO) Scale for Pruritus

- Used to measure patients' scratching as observed by their caregiver twice daily (once in the morning and once in the evening)
- Scratching was assessed on a 5 point scale (0-4):
  - 0: none
  - 1: mild
  - 2: moderate
  - 3: severe
  - 4: very severe

Appendix F: General Information

- Initial care for patients with PFIC targets symptoms and nutritional problems, including fat-soluble vitamin supplementation.
- Ursodiol is usually considered first line therapy for all PFIC types and has been proven to improve liver function and pruritus. Use of Ursodiol is supported by expert opinion; additionally, in the pivotal MARCH-PFIC study, 85% of placebo and 83% of Livmarli patients were already receiving Ursodiol.
- Off-label conventional treatment for PFIC pruritus includes antihistamines, rifampin, and cholestyramine. In the pivotal MARCH-PFIC study, 50% of placebo and 55% of Livmarli patients were already receiving rifampin.
- Other PFIC options include surgical options such as nasobiliary drainage, partial external biliary diversion, and liver transplant.

- Livmarli will not work on PFIC type 2 with ABCB11 variants that encode for absence of BSEP-3 since Livmarli acts on the bile acid transporter. Therefore, in patients missing the BSEP-3 transporter, Livmarli may not inhibit the bile salt export pump.

Appendix G: Genetic Confirmation of PFIC

	PFIC 1	PFIC 2	PFIC 3	PFIC 4	PFIC 5	PFIC 6	PFIC (no #)
Protein deficiency	FIC 1	BSEP	MDR3	TJP2	FXR	MYO5B	USP53
Mutated gene	ATP8B1	ATP8B11	ABCB4	TJP2	NR1H4	MYO5B	USP53

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 PO daily
Maintenance: 380 mcg/kg/day PO daily

<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="7">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="5">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 rowspan="2">3</td><td>2.5</td></tr>
<tr><td>70 or higher</td><td>1.5</td><td>3</td></tr>
</table>
</td><td>380 mcg/kg/day, up to a maximum of 28.5 mg/day (3 mL/day)</td></tr>
<tr><td>PFIC</td><td>Starting dose: 285 mcg/kg PO once daily
Maintenance dose: dose should be increased to 285 mcg/kg PO twice daily, 428 mcg/kg PO twice daily, and then to 570 mcg/kg PO twice daily, as tolerated

Volume per dose (mL) by patient weight</td><td>1,140 mcg/kg/day up to a maximum of 38 mg/day (4 mL/day)</td></tr>
</table>

Indication	Dosing Regimen	Maximum Dose

Patient weight (kg)	285 mcg/kg	428 mcg/kg	570 mcg/kg
10 to 12	0.35	0.5	0.6
13 to 15	0.4	0.6	0.8
16 to 19	0.5	0.8	1
20 to 24	0.6	1	1.25
25 to 29	0.8	1.25	1.5
30 to 34	0.9	1.5	2
35 to 39	1.25	1.5	2
40 to 49	1.25	2	2
50 to 59	1.5	2	2
60 or higher	2	2	2

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 2024. Available at: https://livmarlihcp.com/. Accessed March 27, 2024.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2023. Available at: https://www.clinicalkey.com/pharmacology/. Accessed March 27, 2024.

Alagille Syndrome

3. 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 April 27, 2023.
4. 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.
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Progressive Familial Intrahepatic Cholestasis

7. Davit-Spraul A, Gonzales E, Baussan C, and Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet Journal of Rare Diseases. 2009; 4:1. doi:10.1186/1750-1172-4-1.

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9. Baker A, Kerkar N, Todorova L, Kamath BM, and Houwen RHJ. Systematic review of progressive familial intrahepatic cholestasis. Clinics and Research in Hepatology and Gastroenterology. 2019; 43: 20-36.
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12. ClinicalTrials.gov. A study to evaluate the efficacy and safety of Maralixibat in subjects with progressive familial intrahepatic cholestasis (MARCH-PFIC). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT03905330. Accessed March 27, 2024.

Reviews, Revisions, and Approvals	Date
Policy created	07/2022
3Q 2023 annual review: updated criteria to reflect pediatric extension to age ≥ 3 months; added Appendix E containing ItchRO scale since criteria requires at least moderate scratching; references reviewed and updated.	07/2023
RT4: criteria updated with newly approved indication for PFIC: modified age restriction, removed minimum body weight restriction, and updated limitation of use and contraindications per FDA labeling; references reviewed and updated.	04/2024