Clinical Policy: Maralixibat (Livmarli)

Reference Number: CP.PHAR.543
Effective Date: 09.29.21
Last Review Date: 08.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® 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. Member does not have portal hypertension or history of a hepatic decompensation event;
7. Failure of ursodeoxycholic acid, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for ursodeoxycholic acid*
8. 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;
9. Documentation of member's current body weight in kilograms (kg);
10. 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);
   a. Has moderate to severe pruritis (e.g., ≥ 2 on 0 to 4 scale);
   b. 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. Member does not have portal hypertension or history of a hepatic decompensation event;
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. Livmarli is not prescribed concurrently with other IBAT inhibitors (e.g., Bylvay™);
9. Documentation of member's current body weight in kg;
10. 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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by an improvement in pruritus;
3. Documentation of member's current body weight in kg;
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. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in <u>any</u> 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

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 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

- 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="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="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

<table>
<tr><th colspan="4">Volume per dose (mL) by patient weight</th></tr>
<tr><th>Patient weight (kg)</th><th>285 mcg/kg</th><th>428 mcg/kg</th><th>570 mcg/kg</th></tr>
<tr><td>10 to 12</td><td>0.35</td><td>0.5</td><td>0.6</td></tr>
<tr><td>13 to 15</td><td>0.4</td><td>0.6</td><td>0.8</td></tr>
<tr><td>16 to 19</td><td>0.5</td><td>0.8</td><td>1</td></tr>
<tr><td>20 to 24</td><td>0.6</td><td>1</td><td>1.25</td></tr>
<tr><td>25 to 29</td><td>0.8</td><td>1.25</td><td>1.5</td></tr>
</table>
</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	
	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 May 13, 2024.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2024. Available at: https://www.clinicalkey.com/pharmacology/. Accessed May 28, 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 May 29, 2024.
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.
5. Turnpenny PD and Ellard S. Alagille syndrome: pathogenesis, diagnosis, and management. Eur J Hum Genet. 2012 Mar; 20(3): 251–257.
6. Gonzales E, Hardikar W, Stormon M, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a 7andomized phase 2 study. Lancet. 2021 Oct 30; 398(10311): 1581-1592.

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.
8. Gunaydin M and Cil A. Progressive familial intrahepatic cholestasis: Diagnosis, management, and treatment. Hepatic Medicine: Evidence and Research. 2018; 10: 95-104.
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.
10. Hirschfield GM, Heathcote EJ, and Gerswhin ME. Pathogenesis of cholestatic liver disease and therapeutic approaches. Reviews in Basic and Clinical Gastroenterology and Hepatology. 2010; 139(5): 1481-1496.
11. Progressive Familial Intrahepatic Cholestasis Advocacy and Resource Network. Diagnosis and treatment. Available at: https://www.pfic.org/diagnosis-and-treatment-of-pfic/. Accessed May 29, 2024.

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 May 29, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	06.01.21	08.21
Drug is now FDA approved - criteria updated per FDA labeling: added maximum daily dose per PI; added requirement for documentation of member's weight in kg; references reviewed and updated.	10.12.21	11.21
3Q 2022 annual review: corrected maximum daily dose from 1 bottle per day to 3 mL per day; modified required pruritis from medium to moderate scratching to align with verbiage from the Itch Reported Outcome score used in the ICONIC trial; references reviewed and updated.	05.04.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.05.22	
RT4: updated FDA-approved indication for pediatric extension from 1 year to 3 months of age and older.	04.05.23	
3Q 2023 annual review: added Appendix E containing ItchRO scale since criteria requires at least moderate scratching; references reviewed and updated.	04.27.23	08.23
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.	03.27.24	
3Q 2024 annual review: for initial criteria, added exclusions for portal hypertension and history of a hepatic decompensation event for both PFIC and ALGS per competitor analysis and to align with other PFIC and ALGS criteria; references reviewed and updated.	05.13.24	08.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.