Original Effective Date: 02/01/2022
Current Effective Date: 03/28/2024
Last P&T Approval/Version: 01/31/2024
Next Review Due By: 01/2025
Policy Number: C22224-A

Livmarli (maralixibat)

PRODUCTS AFFECTED

Livmarli (maralixibat)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Cholestatic pruritus in patients with Alagille syndrome (ALGS)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. CHOLESTATIC PRURITUS:
1. Documented diagnosis of Alagille syndrome
   AND
2. Documentation of ONE of the following that support the diagnosis [DOCUMENTATION

REQUIRED]:
(a) Clinical features with involvement in 3 of 7 main organ systems (hepatic, ocular, skeletal, vascular, facial, cardiac or renal) or
(b) Liver biopsy showing bile duct paucity or
(c) Use of an approved genetic test showing mutation/deletion of 1 of 2 known genes (JAG1, NOTCH2)
AND

3. Documentation of members symptoms of moderate to very severe pruritus
AND
4. Prescriber attests to obtaining baseline liver tests, fat-soluble vitamin levels, and hydration status, and monitoring during treatment as recommended per FDA label
AND
5. Prescriber attests, or the clinical reviewer has found, the member has no clinical evidence of decompensated cirrhosis
AND
6. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary alternatives for the given diagnosis (see BACKGROUND). Documentation of medication(s) tried, dates of trial(s) and reason for treatment failure(s) is required.

CONTINUATION OF THERAPY:

A. CHOLESTATIC PRURITUS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in pruritus
AND
4. Prescriber attests to continued monitoring of liver tests, fat-soluble vitamin levels, and hydration status during treatment as recommended per FDA label

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified gastroenterologist or hepatologist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

3 months of age and older

QUANTITY:

Start dosing at 190 mcg/kg administered orally once daily; after one week, increase to 380 mcg/kg once daily, as tolerated.
Maximum daily dose volume for patients above 70kg is 3 mL/ 28.5 mg per day; 90ml per dispense

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Ileal Bile Acid Transporter (IBAT) Inhibitors

FDA-APPROVED USES:
Indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 3 months of age and older

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Individual Dose Volume by Patient Weight

Patient Weight (kg)	Days 1-7 (190 mcg/kg once daily)		Beginning Day 8 (380 mcg/kg once daily)	
	Volume QD (mL)	Dosing dispenser size (mL)	Volume QD (mL)	Dosing dispenser size (mL)
5 to 6	0.1	0.5	0.2	0.5
7 to 9	0.15		0.3	
10 to 12	0.2		0.45	
13 to 15	0.3		0.6	1
16 to 19	0.35		0.7	
20 to 24	0.45		0.9	
25 to 29	0.5		1	
30 to 34	0.6	1	1.25	3
35 to 39	0.7		1.5	
40 to 49	0.9		1.75	
50 to 59	1		2.25	
60 to 69	1.25	3	2.5	
70 or higher	1.5		3	

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Alagille syndrome (ALGS) is a rare autosomal dominant genetic disorder caused by pathogenic variants in JAG1 or NOTCH2, which encode fundamental components of the Notch signaling pathway. The specific symptoms and severity of Alagille syndrome can vary greatly from one person to another, even within the same family. Clinical features span multiple organ systems including hepatic, cardiac, vascular, renal, skeletal, craniofacial, and ocular, and occur with variable phenotypic penetrance. Common symptoms, which often develop during the first three months of life, include blockage of the flow of bile from the liver (cholestasis), yellowing of the skin and mucous membranes (jaundice), poor weight gain and growth, and severe itching (pruritis).
Additional symptoms include heart murmurs, congenital heart defects, vertebral (back bone) differences, thickening of the ring that normally lines the cornea in the eye (posterior embryotoxon) and distinctive facial features. Most people with Alagille syndrome have changes (mutations) in one copy of the JAG1 gene. A

small percentage (2 percent) of patients has mutations of the NOTCH2 gene. These mutations can be inherited in an autosomal dominant pattern, but in about half of cases, the mutation occurs as a new change ("de novo") in the individual and was not inherited from a parent. The current estimated incidence of ALGS is approximately 1/30,000 –1/45,000.

Alagille syndrome can be associated with abnormalities of the liver, heart, eyes, skeleton, kidneys and other organ systems of the body. A main finding of Alagille syndrome is liver disease that often becomes apparent within the first three months of life. However, individuals with mild liver involvement may not be diagnosed until later in life. Liver disease in Alagille syndrome, if present, may range in severity from jaundice or mild cholestasis to severe, progressive liver disease that can potentially result in liver failure.

Approximately 90 percent of individuals with Alagille syndrome have a reduced number of bile ducts (bile duct paucity) within the liver. Bile ducts are small tube-like structures that carry bile from the liver to the small intestines. The formation of bile is one of the functions of the liver. Bile is a fluid that contains water, certain minerals that carry an electric charge (electrolytes), and other materials including bile salts, phospholipids, cholesterol, and an orange-yellow pigment (bilirubin) that is a byproduct of the natural breakdown of the hemoglobin of red blood cells. Bile flow accomplishes two important tasks within the body: it aids in digestion and absorption of dietary fats, vitamins, and other nutrients and helps eliminate excess cholesterol, bilirubin, waste, and toxins from the body.
Therefore, a problem with bile flow often results in malabsorption of vital nutrients and the accumulation of toxic materials in the body.

Because of the reduced number of bile ducts, individuals with Alagille syndrome can develop jaundice and cholestasis usually during the first four months of life. Cholestasis refers to reduced or obstructed flow of bile from the liver. Cholestasis can cause yellowing of the skin (jaundice) or whites of the eyes (icterus), itching (pruritus) that may be intense, pale-colored stools, dark urine, fatty bumps (xanthomas) just under the surface of the skin, and an abnormally enlarged liver (hepatomegaly) and/or enlarged spleen (splenomegaly). Because the body cannot properly absorb fats and fat-soluble vitamins (vitamins A, D, E, and K), affected children may also experience growth deficiencies and failure to thrive. Malabsorption of vital nutrients can also lead to rickets, a condition marked by softened, weakened bones (vitamin D deficiency), vision problems (vitamin A deficiency), poor coordination and developmental delays (vitamin E deficiency) and blood clotting problems (vitamin K deficiency).

In approximately 15 percent of patients, progressive liver disease results in scarring of the liver (cirrhosis) and liver failure. There is no way to tell which children are at risk for serious, progressive liver disease in Alagille syndrome.

Many individuals with Alagille syndrome have heart (cardiac) abnormalities that can range from benign heart murmurs to serious structural defects. A heart murmur is an extra sound that is heard during a heartbeat. Heart murmurs in children with Alagille syndrome are usually caused by narrowing of the blood vessels of the lungs (pulmonary artery stenosis). The most common heart abnormality is peripheral pulmonary stenosis in which some of the blood vessels carrying blood to the lungs (pulmonary arteries) are narrowed (stenosis). Some children with Alagille syndrome may have complex heart defects, the most common of which is tetralogy of Fallot. Tetralogy of Fallot is a rare form of cyanotic heart disease. Cyanosis is abnormal bluish discoloration of the skin and mucous membranes that occurs due to low levels of circulating oxygen in the blood.
Tetralogy of Fallot consists of a combination of four different heart defects: ventricular septal defect, obstructed outflow of blood from the right ventricle to the lungs due to an abnormal narrowing of the

opening between the pulmonary artery and the right ventricle of the heart (pulmonary stenosis), displaced aorta that causes blood to flow into the aorta from both the right and left ventricles, and abnormal enlargement of the right ventricle.

Additional heart defects that can occur in Alagille syndrome include ventricular septal defects, atrial septal defects, patent ductus arteriosus, and coarctation of the aorta. Some studies have shown that in rare cases there is an association with Wolff-Parkinson-White syndrome, a condition characterized by electrical disturbances in the heart. (For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database.)

Some individuals with Alagille syndrome may have eye (ocular) abnormalities, especially posterior embryotoxon, a condition marked by thickening of the ring that normally lines the cornea in the eye. The cornea is the thin, transparent membrane that covers the eyeballs. In most cases, posterior embryotoxon is a benign finding that primarily helps to establish a clinical diagnosis and vision is usually unaffected, although mild decreases in the clarity of vision may occur. Less commonly, other eye abnormalities may occur such as Axenfeld anomaly, a condition in which strands of the iris are abnormally attached to the cornea, or progressive degeneration of the retina (pigmentary retinopathy). The retina is the thin layers of nerve cells that lines that inner surface of the back of the eyes and senses light and converts it to nerve signals, which are then relayed to the brain through the optic nerve.
Individuals with Alagille syndrome usually have distinctive facial features including deeply set and widely spaced (hypertelorism) eyes, a pointed chin, broad forehead, and low-set, malformed eyes. In older individuals and adults, the chin may appear larger and more prominent (prognathia).
Skeletal abnormalities may occur in some individuals with Alagille syndrome including butterfly vertebrae, a condition in which certain bones of the spinal column are irregularly shaped. This condition is often noted on an x-ray, but usually does not cause any symptoms or problems (asymptomatic).
Additional symptoms may occur in some individuals with Alagille syndrome including kidney (renal) abnormalities, pancreatic insufficiency, vascular anomalies, mild developmental delays and cognitive impairment. Kidney abnormalities may be more prevalent in individuals with Alagille syndrome caused by mutations in the NOTCH2 gene and include abnormally small kidneys, the presence of cysts on the kidneys and decreased or impaired kidney function. The pancreas is a small organ located behind the stomach that secretes enzymes that travel to the intestines and aid in digestion. The pancreas also secretes other hormones such as insulin, which helps to break down sugar. Pancreatic insufficiency is when the pancreas cannot produce or transport enough enzymes to the intestines to aid in the breakdown and absorption of food and nutrients.
Individuals with Alagille syndrome can also develop abnormalities of certain blood vessels (vascular anomalies) including those in the brain, liver, lungs, heart, and kidneys. Vascular anomalies in the brain can lead to bleeding inside the brain (intracranial bleeding) and stroke. Some individuals with Alagille syndrome have developed a condition known as Moyamoya syndrome. Moyamoya syndrome is a progressive disorder that is characterized by narrowing (stenosis) and/or closing (occlusion) inside the skull of the carotid artery, the major artery that delivers blood to the brain.
Intracranial bleeding and other vascular anomalies are potentially life-threatening complications and account for a significant percentage of mortality and morbidity in Alagille syndrome.

Medical management is supportive, focusing on specific symptoms of disease. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, gastroenterologists, cardiologists, ophthalmologists, and other healthcare professionals may need to systematically and comprehensively plan an affect child’s treatment. Individuals with Alagille syndrome should have a baseline echocardiogram (ultrasound of the heart) to screen for heart involvement, ultrasound of the abdomen to screen for liver

and kidney anomalies, and a screening eye (ophthalmology) exam, In addition, if not previously obtained for specific symptoms, a screening imaging study of the blood vessels of the head (MRI/MRA) is recommended for children who are old enough to sit through the study without need for anesthesia or sedation. Supplemental treatment with vitamins and nutrients is essential for individuals with malabsorption. Such treatment may include restoring vitamins A, D, E and K. Young children may be given formula with medium chain triglycerides because this form of fat is better absorbed by individuals with Alagille syndrome who have cholestasis. Some affected children may need to receive extra calories through a tube that runs from the nose to the stomach (nasogastric tube) or through a tube placed directly into the stomach through a small incision in the abdominal wall and stomach (gastrostomy tube).

Specific treatment may be indicated for individuals with cholestatic liver disease. The drug ursodeoxycholic acid is given to help improve bile flow, which can lead to a reduction in some symptoms such as itching (pruritus) or cholesterol deposits (xanthomas). However, pruritus associated with Alagille syndrome often is resistant to therapy. Additional drugs that have been used to treat pruritus include antihistamines, rifampin, cholestyramine, and naltrexone. Keeping the skin properly hydrated with moisturizers is also recommended. Cholestyramine may also be indicated for individuals with elevated cholesterol levels or xanthomas.

Some affected infants and children with Alagille syndrome who do not respond to drug and dietary therapies may be treated by a surgical procedure known as partial biliary diversion. This surgical procedure is used to disrupt or divert recirculation of bile acids between the liver and the gastrointestinal tract. This therapy has demonstrated that, in some children, it can improve certain symptoms such as reducing itchiness or xanthoma formation.

In severe cases of Alagille syndrome (i.e., cases that have progressed to cirrhosis or liver failure or in which other therapies were unsuccessful), liver transplantation may be required.

Additional complications that can be associated with Alagille syndrome including heart, blood vessel and kidney abnormalities are treated in the standard manner. In some cases, this may include surgery.

In March 2023, based on positive data from the phase 2 RISE study, the indication for Livmarli was expanded to include infants as young as 3 months with cholestatic pruritis with ALGS. The RISE study evaluated the safety and tolerability of Livmarli in infants less than 1 year of age with ALGS or PFIC. Patients received 380 mcg/kg once daily.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Livmarli (maralixibat) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Livmarli (maralixibat) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:

- None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Livmarli SOLN 9.5MG/ML

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Other Special Considerations	Q1 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Age Restrictions FDA-Approved Uses Background References	Q2 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Contraindications/Exclusions/Discontinuation Other Special Considerations References	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file