maralixibat (Livmarli™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO250

Description

Maralixibat (Livmarli) is an orally administered reversible ileal bile acid transporter (IBAT) inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: Six months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
maralixibat (Livmarli)	9.5 mg/mL solution	Cholestatic pruritis in patients with Alagille Syndrome one year of age and older	Monthly quantity to allow for a maximum of 380 mcg/kg/day (maximum of 3 mL)

Initial Evaluation

I. **Maralixibat (Livmarli)** may be considered medically necessary when the following criteria are met:
   A. Member is one year of age or older; **AND**
   B. Documentation of member's weight, measured within past three months; **AND**
   C. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**
   D. A diagnosis of **Alagille Syndrome** when the following are met:
      1. Provider attestation member has cholestasis including at least one of the following:
         i. Total serum bile acids greater than three times the upper limit of normal for age; **OR**
         ii. Conjugated bilirubin greater than 1 mg/dL; **OR**
         iii. Unexplained fat-soluble vitamin deficiency; **OR**
         iv. Gamma glutamyl transferase (GGT) greater than three times the upper limit of normal for age; **OR**
         v. Intractable pruritis explainable only by liver disease; **AND**
      2. Diagnosis is confirmed by a molecular genetic test; **OR**
         i. Diagnosis is confirmed by evidence of bile duct paucity on liver biopsy; **AND**
            a. Provider attestation ALGS is present in a first degree relative; **OR**
            b. Provider attestation member has presence of 3 or more clinical features of the disease (e.g., cholestasis, consistent cardiac, renal,

ocular disease, butterfly vertebrae, or characteristic Alagille facies); **AND**

E. Member does not have decompensated cirrhosis or prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy); **AND**
F. Provider attestation member has moderate to severe pruritis; **AND**
G. Treatment with all the following have been ineffective, contraindicated, or not tolerated:
    1. Ursodiol; **AND**
    2. Bile acid sequestrant (e.g., cholestyramine, colesevelam); **AND**
    3. Rifampin; **AND**
    4. Opioid antagonist (e.g., naltrexone); **AND**
    5. Serotonin inhibitor (e.g., sertraline, ondansetron)

I. Maralixibat (Livmarli) is considered investigational when used for all other conditions, including but not limited to:
    A. ALGS in patients less than 12 months of age
    B. Progressive familial intrahepatic cholestasis (PFIC)
    C. Benign recurrent intrahepatic cholestasis 1 and 2 (BRIC1 and BRIC2)
    D. Biliary atresia (BA)
    E. Primary sclerosing cholangitis (PSC)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in pruritis, quality of sleep); **AND**
IV. Member has not had a liver transplant since the last prior authorization period; **AND**
V. Member has not progressed to decompensated cirrhosis or experienced hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy)

Supporting Evidence

I. Alagille Syndrome (ALGS) is a rare, genetic, autosomal dominant disorder, caused by mutations in the genes encoding jagged1 (JAG1) or neurogenic locus notch homolog protein 2 (NOTCH2), both involved in the Notch signaling pathway. It is a multisystem disorder affecting the liver,

cardiovascular system, skeleton, face and eyes. Phenotypic presentation of the disease is variable; however, complications can include cholestasis, pruritis, progressive liver disease, failure to thrive, and xanthomas, all of which lead to liver transplantation. Pruritis is the hallmark symptom of this disease and is thought to be caused by a buildup of pruritogens that accompany bile acids. Bile acid buildup occurs due to impaired development of bile ducts leading to bile duct paucity (reduction of interlobular bile ducts).

II. Maralixibat (Livmarli) is FDA-approved for the treatment of cholestatic pruritis associated with ALGS in patients one year of age and older. The age of presentation ranges from 16 weeks to 10 years and most patients are diagnosed in the first year of life. The maralixibat (Livmarli) clinical trial program did not evaluate patients < 12 months of age; therefore, drug safety and efficacy in this population has not been established.

III. Diagnosis of ALGS is based on a combination of clinical features of the disease, lab findings, imaging, genetic testing, and liver biopsy. Clinical features include hepatic manifestations such as chronic cholestasis and bile duct paucity, characteristic facial features (deep-set eyes and a flat nasal bridge), ophthalmic abnormalities, skeletal involvement, cardiovascular, and renal abnormalities. Cholestasis occurs in 87-100% of patients but may present as mild or not clinically identifiable in certain cases of ALGS. The most sensitive test to confirm cholestasis is via elevations in fasting serum bile acids (normal levels depend on age but are usually <20 umol/L); however, this may not be readily available. Other biomarkers that can be used to confirm cholestasis are elevated gamma glutamyl transferase (GGT) levels (normal levels depend on age but are usually < 200 IU/L) and conjugated/direct serum bilirubin levels (normal levels are usually less than 0.3 mg/dL). Additionally, cholestasis may be suspected in patients experiencing unexplained fat-soluble vitamin deficiency or intractable pruritis explainable only by liver disease. Patients affected with ALGS often present with multiple elevated biomarkers of cholestasis and peak values include bile acid levels> 100 times normal, total bilirubin > 20 mg/dL, and GGT > 2,000 U/L.

IV. Molecular generic test is considered confirmatory for ALGS syndrome. Majority of patients have mutations in JAG1 (94%) with only a small subset (<1%) having mutations in NOTCH2. Additionally, mutations that are variants of unknown significance can also cause ALGS. Genetic evaluation for JAG1 and NOTCH2 mutations is currently available on a commercial basis, though screening for NOTCH2 is limited to a small number of locations at this time.

V. If patients are not screened for ALGS using a genetic test or if JAG1 or NOTCH2 mutations are not identified, patients may be diagnosed using a combination of clinical criteria, liver biopsy which screens for bile duct paucity, and presence of ALGS in first degree relatives. Bile duct paucity is one of the most common characteristics of ALGS and occurs in 90% of patients; however, it may not be present in many patients younger than six months of age and may not be present in mild disease presentation. Bile duct paucity is determined using a ratio of bile ducts to portal tracts of less than 0.5 in a liver biopsy with an adequate number (10) of portal

tracts present. The normal number of bile ducts in a portal tract increases throughout the first years of life, reaching a normal ratio of nearly 2 by adolescence.

VI. Diagnostic Criteria for Alagille Syndrome:

ALGS in a first degree relative	Paucity	JAG1 or NOTCH2 mutation*	Number of criteria needed**
Present or absent	Present	Identified	Any or no features
None (proband)	Present	Not identified	3 or more features
None (proband)	Absent or unknown	Not identified	4 or more features
None (proband)	Absent or unknown	Identified	1 or more features
Present	Present	Not identified	1 or more features
Present	Absent or unknown	Not identified	2 or more features
Present	Absent or unknown	Identified	Any or no features

*Not identified = not identified on mutation screening, or not screened for

** Major clinical criteria include cholestasis, consistent cardiac, renal, ocular disease, butterfly vertebrae, or characteristic Alagille facies of childhood or adulthood

VII. Maralixibat (Livmarli) was not studied in patients with decompensated cirrhosis or in patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). Due to unknown safety and efficacy in this population, maralixibat (Livmarli) should be permanently discontinued if patients progress to portal hypertension or experience a hepatic decompensation event. Additionally, maralixibat (Livmarli) is associated with causing liver test abnormalities and may or may not exacerbate liver injury in patients with severe liver disease (e.g., decompensated cirrhosis, portal hypertension). More studies are needed in this setting to confirm drug safety in significant liver disease.

VIII. Majority of patients with ALGS receive liver transplantation before they reach adulthood. Intractable pruritis is a reason for evaluation for liver transplantation and placement on transplant list, regardless of the extent of direct liver involvement from ALGS. Majority of liver transplants in ALGS are considered successful with most patients alive without a need for re-transplantation. It is considered a curative treatment for the symptoms of pruritis. Therefore, maralixibat (Livmarli) is not expected to be medically necessary in patients with liver transplants as these patients would likely be cured of pruritis.

IX. Severe cholestatic pruritis occurs in up to 45% of patients with ALGS and has negative impacts on quality of life. Itching is often described as the most burdensome symptom of ALGS. According to one study evaluating the burden of ALGS and pruritis among 26 patients and 24 caregivers, 15% of patients experienced severe itching, 31% experienced moderate itching, 24% experienced mild itching, and 27% experienced very mild itching. Pivotal trial evaluating maralixibat (Livmarli) studied patients with moderate to severe pruritis at baseline as measured by the ItchRO(Obs) score. The value of maralixibat (Livmarli) in patients with mild pruritis has not been established and the drug may be medically necessary only in patients with history of

significant scratching or medium scratching at baseline, consistent with moderate to severe pruritis presentation.

X. Treatment of ALGS is aimed at maintaining optimal nutrition, preventing fat-soluble vitamin deficiencies, addressing pruritis, improving bile flow, and treating any extrahepatic features. There are no FDA approved agents for pruritis associated with ALGS except for maralixibat (Livmarli) at this time; however, there are agents that are commonly used off-label. For relief of pruritis unresponsive to antihistamines, ursodeoxycholic acid, rifampin, bile-acid sequestrants, naltrexone, and sertraline may be used. Antihistamines should not be exclusive therapy but can be dosed at night when pruritis interferes with sleep. Treatment response to pharmacological agents is often unpredictable; however, depending on the degree of pruritis, some experience relief of pruritis symptoms. Patients refractory to pharmacological therapy may undergo partial external biliary diversion or ileal exclusion surgery to remove excess bile prior to liver transplantation.

XI. There is lack of robust studies of standard of care agents (ursodiol, bile acid sequestrants, rifampin, naltrexone, sertraline) in the treatment of ALGS; however, evidence related to pruritis is available from studies in other cholestatic disease states, retrospective and open-label ALGS studies, and historical treatment experience with the drugs. Trial of all standard of care agents prior to maralixibat (Livmarli) is both a cost effective and clinically appropriate strategy as each drug exerts effects on pruritis via distinct therapeutic pathways and inefficacy with one or more agent(s) does not confer inefficacy with subsequent drugs.

- **Ursodiol** - commonly used as the first-line treatment option due to its anti-cholestatic properties which are exerted by improved hepatobiliary secretory function and reduced bile toxicity. It is the only medication that may affect liver disease progression and is recommended by the European Association for the Study of the Liver (EASL) guidelines as the initial pharmacological treatment for cholestatic pruritis. Additionally, several rare disease organizations such as The Childhood Liver Disease Research Network and National Organization for Rare Disorders (NORD) and expert reviews recommend ursodiol as first line in patients with ALGS. The effect of ursodiol on pruritis is an area that requires more research; however, an open-label study, retrospective cohort study, and case reports note positive treatment response in pediatric patients with ALGS and other intrahepatic liver diseases (Kronsten, 2013; Narkewicz, 1998;).
- Subsequent treatment options are aimed at reducing symptoms of pruritis. Pruritis can be a feature of any cholestatic disease, thus there are many treatment options available with variable evidence.
- **Bile acid sequestrant** - cholestyramine is FDA-approved for the treatment of pruritis associated with cholestasis in adults and is often used as one of the first-line treatment options for pediatric patients with pruritis associated with cholestasis. Despite a limited evidence base, cholestyramine is listed as a treatment option for

ALGS by The Childhood Liver Disease Research Network and NORD and is recommended first-line by EASL guidelines for the treatment of pruritis associated with cholestasis. There is additionally one retrospective study indicating efficacy in some patients. The lack of evidence is largely because the agent entered widespread use before the era of evidence-based medicine. Additionally, colestipol and colesevelam have also been evaluated in the treatment of pruritis and are generally better tolerated than cholestyramine (Cies, 2007; Kronsten, 2013).

- **Rifampin** - commonly used after treatment failure with ursodiol/cholestyramine and is recommended for the treatment of cholestatic pruritis by EASL guidelines, rare disease organizations, and expert reviews. Additionally, there are various reports in literature showing positive results on pruritis due to chronic cholestasis, including retrospective, case controlled, and prospective trials in other cholestatic diseases in children and adults. For example, one meta-analysis of five randomized prospective controlled trials in adults and children concluded that rifampin is safe and effective for treatment of pruritis in patients with cholestasis associated with chronic liver diseases (majority of patients had primary biliary cirrhosis). Additionally, one prospective study, one retrospective study, and cases reports are also available in patients with ALGS (Khurana, 2006; Yerushalmi, 1999; Kronsten, 2013).
- **Opioid antagonist** - naltrexone is recommended for the treatment of pruritis associated with cholestatic liver disease by the EASL guidelines as a subsequent option for patients failing cholestyramine and rifampin and is mentioned by expert reviews and rare disease organizations (NORD). Efficacy is supported by a meta-analysis which concluded that opioid antagonists significantly reduced cholestasis-related pruritis (Tandon, 2007). Safety and efficacy of naltrexone in children is scarce; however, naltrexone can be safely used by pediatric patients with cholestatic liver disease and its use has been described in a retrospective study, case reports and case series in patients with ALGS (Kronsten, 2013; Zellos, 2010; Mozer-Glassberg, 2011).
- **Serotonin Inhibitors** - EASL guidelines recommended sertraline as a fourth-line treatment option for patients with cholestatic pruritis. Efficacy and safety are supported by one randomized double-blind, placebo-controlled study in patients with pruritis due to liver disease (Mayo, 2007) and one prospective multicenter study in children with refractory cholestatic pruritis related to PFIC and Alagille syndrome (Thebaut, 2017). Ondansetron has been studied in several cholestatic liver diseases with mixed results. One placebo-controlled trial studied intravenous ondansetron in adult patients with cholestatic pruritis and showed improvement in itch intensity by 50%. Another randomized, double-blind cross over study determined there was significant but moderate reduction in visual analogue scale (VAS) score when ondansetron was compared to placebo in patients with chronic

liver disease. Another study showed that ondansetron therapy effectively reduced pruritis in 5 out of 13 patients; however, the reduction in itch intensity did not correlate to substantial decrease in objective scratching activity. A fourth clinical trial compared ondansetron to placebo and found no significant differences in pruritis scores or scratching activity (Ebhohon, 2023).

XII. Maralixibat (Livmarli) was studied in a pivotal Phase 2b, double-blind, placebo-controlled, randomized drug withdrawal (RWD) trial ICONIC, two randomized, double-blind, placebo-controlled Phase 2 trials ITCH and IMAGO, as well as ongoing open-label trial MERGE. The pivotal study included 31 pediatric patients (median age: 5.4 years) with ALGS (JAG1 mutation: 100%), native liver, elevated serum bile acids (mean: 283umol/L), and moderate to severe pruritis (mean weekly average ItchRO(Obs) score: 2.9). At baseline, patients were treated with standard of care agents (ursodeoxycholic acid: 81%; rifampin 74%; naltrexone: 3%; sertraline: 3%) that were continued during the trial. Patients were excluded if they had prior surgical interruption of the enterohepatic circulation, liver transplantation, and decompensated cirrhosis. The primary endpoints were the least square (LS) mean change in serum bile acid (sBA) levels and LS mean difference in pruritis severity as measured by the ItchRO(Obs) score between maralixibat (Livmarli) and placebo during the RWD period. Both endpoints met statistical significance and it was determined that there were substantial number of patients experiencing clinically meaningful change in pruritis scores while on treatment with maralixibat (Livmarli).

XIII. Pooled safety data is available in 86 patients with ALGS with median duration of exposure of 32.3 months. Most common (≥5%) any grade adverse events (AE) included diarrhea (55.8%), abdominal pain (53.5%), vomiting (40.7%), fat-soluble vitamin deficiency (25.6%), transaminases increased (18.6%), gastrointestinal bleeding (10.4%), bone fractures (9.3%), and nausea (8.1%). Three patients experienced vomiting as a serious AE requiring hospitalization or intravenous fluid administration. Treatment interruptions or dose reduction occurred in 5 (6%) patients due to diarrhea, abdominal pain, or vomiting. Seven (8.1%) patients discontinued due to ALT increase. There are no black box warnings or contraindications at this time. Warnings and precautions include liver test abnormalities, gastrointestinal adverse reactions, and fat-soluble vitamin deficiency.

Investigational or Not Medically Necessary Uses

I. Maralixibat (Livmarli) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. ALGS in patients < 12 months of age
      i. Maralixibat (Livmarli) is being studied in one open-label, single-arm, Phase 2 trial in patients < 12 months of age with ALGS or progressive familial intrahepatic cholestasis (PFIC). The primary outcome of the study is the frequency of

treatment-emergent adverse events, and a secondary outcome in change in fasting serum bile acids (sBA) levels. Study results are not available at this time. Study completion date is expected in January 2023 (NCT04729751).

B. Progressive familial intrahepatic cholestasis (PFIC)
    i. Maralixibat (Livmarli) is being studied in one randomized, double-blind, placebo-controlled Phase 3 study in patients with PFIC. The primary outcome studied is the mean change in pruritis as assessed by ItchRO(Obs) score. Secondary outcomes include treatment response and mean change in serum bile acids. Study results are not available at this time. Study completion date is expected in July 2022 (NCT03905330).
    ii. Maralixibat (Livmarli) is being studied in one open-label, single-arm, Phase 2 trial in patients < 12 months of age with ALGS or PFIC. The primary outcome of the study is the frequency of treatment-emergent adverse events, and a secondary outcome in change in fasting serum bile acids (sBA) levels. Study results are not available at this time. Study completion date is expected in January 2023 (NCT04729751).

C. Benign recurrent intrahepatic cholestasis 1 and 2 (BRIC1 and BRIC2)
    i. BRIC1 and BRIC2 are milder versions of PFIC1 and PFIC2. BRIC1 and 2 occur on the same genes as PFIC1 and 2, respectively. However, cholestatic events are described as recurrent and unpredictable. Cholestatic episodes often last for a couple of weeks, vary in severity and duration and do not progress to liver failure. Therefore, there is uncertainty whether the duration of disease would offset treatment benefit. Further research and collection of evidence in patients with BRIC1 and BRIC2 is warranted at this time. There are no ongoing clinical trials of maralixibat (Livmarli) in patients with BRIC1 or BRIC2

D. Biliary atresia (BA)
    i. BA is a rare condition presenting in infants in which the bile ducts outside and inside the liver are scarred and blocked, impeding bile flow. The cause is largely unknown and can include viral, toxic, immunologic and generic etiologies. Maralixibat (Livmarli) is being studied in infants with BA after Hepatoportoenterostomy (also known as the Kasai procedure) in a Phase 2, double-blind, randomized, placebo-controlled study. The primary endpoint evaluated is the mean change in total serum bilirubin levels; secondary endpoints include changes in serum bile acid (sBA) levels, and time to liver transplantation or death. Study results are not available at this time. Study completion date is expected in August 2024 (NCT04524390).

E. Primary sclerosing cholangitis (PBC)
    i. PBC is a rare, chronic, progressive, autoimmune, cholestatic liver disease characterized by damage to intrahepatic bile ducts. Maralixibat (Livmarli) was

studied in a phase 2, randomized, placebo-controlled trial in 66 patients aged 18-80 years with PBC and significant pruritis. The primary outcome was change in Adult Itch Reported Outcome (ItchRO) average weekly sum score (0, no itching; 70, maximum itching) from baseline to week 13/early termination (ET). Mean ItchRO weekly sum scores decreased from baseline to week 13/ET with maralixibat (Livmarli) (–26.5; 95% confidence interval [CI], –31.8, –21.2) and placebo (–23.4; 95% CI, –30.3, –16.4). The difference between groups was not significant (P = 0.48). Due to non-statistically significant results, maralixibat (Livmarli) was not associated with improvements in pruritis when compared to placebo and more studies are needed to evaluate this therapy in PBC.

Appendix

I. Maralixibat (Livmarli) Individual Dose Volume by Patient Weight

Member weight (kg)	Days 1-7 (190 mcg/kg/day)	Beginning Day 8 (380 mcg/kg/day)	PA#1: quantity per 28-day supply for month one (mL)	PA#2: quantity per 28-day supply for month two through six (mL)	Renewal: quantity per 28-day supply
	Volume QD (mL)	Volume QD (mL)			
5 to 6	0.1	0.2	4.9	5.6	5.6
7 to 9	0.15	0.3	7.4	8.4	8.4
10 to 12	0.2	0.45	10.9	12.6	12.6
13 to 15	0.3	0.6	14.7	16.8	16.8
16 to 19	0.35	0.7	17.2	19.6	19.6
20 to 24	0.45	0.9	22.1	25.2	25.2
25 to 29	0.5	1	24.5	28	28
30 to 34	0.6	1.25	30.5	35	35
35 to 39	0.7	1.5	36.4	42	42
40 to 49	0.9	1.75	43.1	49	49
50 to 59	1	2.25	54.3	63	63
60 to 69	1.25	2.5	61.3	70	70
70 or higher	1.5	3	73.5	84	84

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease State
odevixibat (Bylvay™)	Progressive familial intrahepatic cholestasis (PFIC); Alagille Syndrome (ALGS)

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Renewal evaluation changed from 12 to six months; added ondansetron as an example of accepted medications in serotonin inhibitor class, updated supportive evidence section, added related policies section.	07/2023
Policy created	02/2022