Ileal Bile Acid Transporter (IBAT) Inhibitors
EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO250

Description
Odevixibat (Bylvay) and maralixibat (Livmarli) are orally administered reversible ileal bile acid transporter (IBAT) inhibitors.

Length of Authorization
- Initial: Six months
- Renewal: Six months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
odevixibat (Bylvay)	Pruritis in patients three months of age and older with progressive familial intrahepatic cholestasis (PFIC)	200 mcg pellets 600 mcg pellets 400 mcg capsules 1200 mcg capsules	Monthly quantity to allow for a maximum of 120 mcg/kg/day (maximum of 6mg/day)
	Cholestatic pruritis in patients 12 months of age and older with Alagille Syndrome (ALGS)		Monthly quantity to allow for a maximum of 120 mcg/kg/day
maralixibat (Livmarli)	Cholestatic pruritis in patients five years of age and older with progressive familial intrahepatic cholestasis (PFIC)	9.5 mg/mL solution in 30mL bottle	Monthly quantity to allow for a maximum of 1,140 mcg/kg/day (maximum of 38 mg or 4 mL per day)
	Cholestatic pruritis in patients with Alagille Syndrome (ALGS) three months of age and older		Monthly quantity to allow for a maximum of 380 mcg/kg/day (maximum of 28.5 mg or 3 mL per day)

Initial Evaluation

I. **Odevixibat (Bylvay)** and **maralixibat (Livmarli)** may be considered medically necessary when the following criteria are met:
   A. Documentation of member's weight, measured within the past three months, is provided; **AND**
   B. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**
      1. A diagnosis of **Progressive Familial Intrahepatic Cholestasis (PFIC)**; **AND**
         i. Diagnosis is confirmed by a molecular genetic test; **AND**

ii. Member does not have PFIC type 2 with ABCB11 variants resulting in nonfunctional or absent bile salt export pump protein (BSEP) as confirmed by a molecular genetic test; **AND**
    a. The request is for odevixibat (Bylvay); **AND**
        i. Member is three months of age or older; **OR**
    b. The request is for maralixibat (Livmarli); **AND**
        i. Member is five years of age or older; **AND**
        ii. Treatment with odevixibat (Bylvay) has been ineffective, not tolerated, or is contraindicated; **OR**

2. A diagnosis of **Alagille Syndrome (ALGS)**; **AND**
    i. Diagnosis is confirmed by a molecular genetic test; **OR**
        a. Diagnosis is confirmed by evidence of bile duct paucity on liver biopsy; **AND**
        b. Provider attestation that Alagille Syndrome (ALGS) is present in a first degree relative; **OR**
            i. Provider attestation that member has presence of three or more clinical features of the disease (e.g., cholestasis, consistent cardiac, renal, ocular disease, butterfly vertebrae, or characteristic Alagille facies); **AND**
    ii. The request is for maralixibat (Livmarli); **AND**
        a. Member is three months of age and older; **OR**
    iii. The request is for odevixibat (Bylvay); **AND**
        a. Member is 12 months of age and older; **AND**
        b. Treatment with maralixibat (Livmarli) has been ineffective, not tolerated, or is contraindicated; **AND**

C. Provider attestation member has cholestasis including at least one of the following:
    1. Total serum bile acids greater than three times the upper limit of normal for age; **OR**
    2. Conjugated bilirubin greater than 1 mg/dL; **OR**
    3. Unexplained fat-soluble vitamin deficiency; **OR**
    4. Gamma glutamyl transferase (GGT) greater than three times the upper limit of normal for age; **OR**
    5. Intractable pruritis explainable only by liver disease; **AND**
D. Other causes of cholestasis have been ruled out (e.g., drug toxicity, hepatitis A, sclerosing cholangitis); **AND**
E. Member does not have decompensated cirrhosis or prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy); **AND**
F. Provider attestation of presence of moderate to severe pruritis; **AND**
G. Treatment with <u>all</u> the following has 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)

II. Odevixibat (Bylvay) and maralixibat (Livmarli) are considered investigational when used for all other conditions, including but not limited to:
   A. Benign recurrent intrahepatic cholestasis (BRIC) 1 and 2
   B. Biliary Atresia
   C. Primary sclerosing cholangitis (PBC)

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. Documentation of member's weight, taken within past three months, is provided; **AND**
V. Member has not had a liver transplant since the last prior authorization period; **AND**
VI. Member has not progressed to decompensated cirrhosis or experience hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy)

Supporting Evidence

Progressive familial intrahepatic cholestasis (PFIC)

I. Progressive familial intrahepatic cholestasis (PFIC) is a group of rare genetic cholestatic diseases which may start early after birth or at a young age and may rapidly progress to end-stage disease. The disease is commonly classified as one of three PFIC 1-3 types depending on the genetic defect, although there may be up to six types. PFIC1 occurs due to mutations on the *ATP8B1* gene. This gene is also expressed in the small intestine, kidney, and pancreas, which explains certain extrahepatic manifestations (e.g., sensorineural deafness). PFIC2 occurs due to mutations on the *ABCB11* gene and PFIC3 is due to reduced expression of multidrug resistance MDR3, which is encoded by *ABCB4* gene.
II. Patients often present with symptoms of cholestasis, growth retardation, increased serum bile acid (BA) blood and liver concentration, jaundice, and pruritis. Cholestasis is an impairment of bile formation and/or bile flow and is caused by absence of transport proteins in PFIC. 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.

III. Pruritis is often described as unrelenting and debilitating, leading to cutaneous wounds and sleep disturbances and is one of the primary causes for surgical treatments and liver transplants. Pruritis is described as mild to moderate in intensity in patients with PFIC3 and as moderate to severe in patients with PFIC1-2. If left untreated, the disease rapidly progresses to liver failure and is associated with early mortality.

IV. Odevixibat (Bylvay) is FDA-approved for the treatment of pruritis associated with PFIC in patients three months of age and older. Age of PFIC onset varies by subtypes where PFIC1 and PFIC2 usually develop during infancy, and PFIC3 develops during late infancy to early adulthood. Symptoms of pruritis may present as early as three months of age.

V. Maralixibat (Livmarli) is FDA-approved in PFIC in patients 5 years of age and older. Age of PFIC onset varies by subtypes where PFIC1 and PFIC2 usually develop during infancy, and PFIC3 develops during late infancy to early adulthood. Symptoms of pruritis may present as early as three months of age.

VI. Progressive familial intrahepatic cholestasis (PFIC) should be considered in patients with cholestasis after ruling out more common causes such as biliary atresia, Alagille syndrome, alpha-1 antitrypsin deficiency, cystic fibrosis, drug toxicity, hepatitis A, sclerosing cholangitis, and extrahepatic bile duct obstruction. Diagnosis takes into account clinical, biochemical, radiological, and histological approaches. Genetic testing may be utilized for supporting a diagnosis of PFIC; however, the clinical phenotype is not always confirmed by genetic testing. This is likely due to other causative genes and/or non-coding regions of known PFIC genes that may contribute to disease manifestation. Approximately one-third of individuals with normal-GGT PFIC lack mutations in *ATP8B1* or *ABCB11* and mutations in *TJP2* explain all of the remaining patients. Additionally, in some patients only one allele of *ATP8B1* or *ABCB11* are detected, making it difficult to distinguish as disease-causing mutations or rare normal variants.

VII. Odevixibat (Bylvay) and maralixibat (Livmarli) are not recommended in patients with BSEP3 variants (subpopulation within PFIC2). Pivotal trials excluded patients with BSEP3 variants as these patients lack a functional BSEP in canalicular member to export bile salts to bile for enterohepatic circulation via biliary excretion. Therefore, the pharmacological effects of odevixibat (Bylvay) and maralixibat (Livmarli) to inhibit the reabsorption of bile salts in the gastrointestinal tract cannot be expected.

VIII. The majority of patients with PFIC 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 PFIC. The majority of liver transplants in PFIC 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,

odevixibat (Bylvay) and maralixibat (Livmarli) are not expected to be medically necessary in patients with liver transplants as these patients would likely be cured of pruritis.

IX. Odevixibat (Bylvay) and maralixibat (Livmarli) were not studied in patients with decompensated cirrhosis or in patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). Odevixibat (Bylvay) and maralixibat (Livmarli) should be permanently discontinued if patients progress to portal hypertension or experiences a hepatic decompensation event. Close monitoring and caution is warranted when initiating treatment in patients with liver disease.

X. According to systematic reviews, around 80% of patients with PFIC have pruritis graded as severe and mild pruritis presentation is less common. PEDFIC1 pivotal trial population consisted of patients with a mean pruritis score of around 3 (a lot of scratching) on a scale from 0 (no scratching) to 4 (worst possible scratching). Additionally, PEDFIC1 inclusion criteria required patients to have a history of significant pruritis and patients were included in the trial if the average scratching score was greater than or equal to 2 (medium scratching) in the 2 weeks prior to baseline. Similarly, in the MARCH-PFIC study the mean pruritis score was 2.9 with inclusion criteria requiring a score of ≥1.5. Therefore, the value of odevixibat (Bylvay) and maralixibat (Livmarli) in patients with mild pruritis has not been established and the drugs may be medically necessary only in patients with history of significant scratching or medium scratching at baseline, consistent with moderate to severe pruritis presentation.

XI. Initial treatment of PFIC addresses nutritional problems and pruritis caused by cholestasis. Treatment response is often unpredictable; however, depending on the degree of pruritis and PFIC type, some patients may respond to pharmacological therapy with standard of care agents. There is lack of randomized controlled studies of standard of care agents in the treatment of PFIC; however, evidence related to pruritis is available from studies in other cholestatic disease states, retrospective PFIC cohort studies, and historical treatment experience with the drugs. Maralixibat (Livmarli) is a newer agent approved for the treatment of PFIC. There's no direct comparative evidence demonstrating superiority of one agent over the other. Trial of all standard of care agents including odevixibat (Bylvay) 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 in PFIC3. However, several rare disease organizations and expert reviews recommend ursodiol regardless of PFIC type. The effect of ursodiol on pruritis is an area that requires more research; however, several open-label and retrospective cohort

studies note positive treatment response in pediatric patients with PFIC and other intrahepatic liver diseases (Narkewicz, 1998; Dinler, 1999; Wanty, 2004).

- 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 sequestrants** - 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 PFIC by the Children's Liver Disease Foundation and is recommended first-line by EASL guidelines for the treatment of pruritis associated with cholestasis. 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).
- **Rifampin** - is commonly used after treatment failure with ursodiol/cholestyramine and is recommended for the treatment of pruritis in pediatric patients with PFIC by EASL guidelines. Additionally, there are various reports in literature showing positive results on pruritis due to chronic cholestasis, including retrospective, case controlled, and prospective trials. One meta-analysis of five randomized prospective controlled trials in adults and children concluded that rifampin is safe and effective for the treatment of pruritis in patients with cholestasis associated with chronic liver diseases (Khurana, 2006).
- **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. 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 case reports and case series (Zellos, 2010; Mozer-Glassberg, 2011; Chang 2008).
- **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. Odevixibat (Bylvay) was studied in PEDFIC1, a Phase 3, double-blind, placebo-controlled, randomized, 24-week trial followed by PEDFIC2, an open-label extension study. PEDIFC1 was conducted in 62 patients with pruritus, aged six months to 17 years, in patients with molecularly confirmed PFIC types 1 and 2. Patients received 40 mcg/kg or 120 mcg/kg odevixibat (Bylvay) dose and were allowed to continue on background treatment (e.g., ursodiol, rifampicin, antihistamines, naltrexone). The primary endpoint was the proportion of positive pruritis assessments (PPAs) as measured by the single-item observer-reported outcome instrument (ObsRo). The secondary endpoint was the change in serum BA from baseline. Both endpoints met statistical significance. Reduction in proportion of pruritis assessments to a score of 0 (no scratching) or 1 (little scratching) from baseline is also deemed clinically meaningful in a patient population refractory to standard of care. The safety data for odevixibat (Bylvay) is available for 69 patients. In PEDFIC1, adverse events (AEs) reported in ≥ 2% of patients at a rate greater than placebo included diarrhea, increased bilirubin and transaminases, vomiting, abdominal pain, and fat-soluble vitamin deficiency. Drug related and liver related AEs occurred at a higher frequency in odevixibat (Bylvay) treated patients than in placebo and included increased ALT (9.5% vs 5%), AST (7.1% vs 5%), bilirubin (9.5% vs 5%), and diarrhea (9.5% vs 5%). No differences in serious AEs were recorded in PEDFIC1. Interim analysis of PEDFIC2 trial show a similar trend with four additional patients reporting serious AEs of cholestasis, acute pancreatitis, splenomegaly, jaundice, hypophagia, and weight decrease. The rate of discontinuation due to adverse events was low.

XIII. Maralixibat (Livmarli) was studied in MARCH-PFIC, a Phase 3, double-blind, placebo-controlled 26-week trial followed by an extension trial MARCH-ON. MARCH-PFIC was conducted in a total of 92 patients, aged ≥12 months and <18 years of age. The median patient age was 4.8 years. The majority of patients enrolled had PFIC2 (n=31), followed by PFIC1 (n=13), PFIC3 (n=9), PFIC4 (n=7), and PFIC6 (n=4). Patients received maralixibat (Livmarli) up to 570 mcg/kg twice daily and were allowed to continue on background treatment (e.g., ursodiol, rifampicin, antihistamines, naltrexone). The primary endpoint was the mean change in the ItchRO (Obs) morning severity score in the PFIC2 cohort between baseline Week 15 through 26. The secondary endpoints included changes in serum BA levels and changes in pruritis and serum BA levels in other PFIC cohorts as well as responder analysis in all cohorts. The primary and secondary endpoints met statistical significance, except proportion of patients in the PFIC2 cohort that were considered

ItchRO (Obs) responders. Clinically meaningful reductions in pruritis scores were observed in patients treated with maralixibat (Livmarli). Safety data is available for all 93 patients followed for 26-weeks as well as data from the long-term extension study. The most common AEs for maralixibat (Livmarli) vs placebo were diarrhea (57% vs 19%), abdominal pain (26% vs 13%), fat-soluble vitamin deficiency (28% vs 35%). The extension study did not report any new safety findings. Fourteen patients (16.5%) experienced a serious AE, with one patient (1.2%) experiencing an AE deemed treatment-related (increased blood bilirubin). Three patients experienced 4 AEs (including diarrhea, bilirubin increase, and ALT increase, and cirrhosis) which led to discontinuation. TEAEs led to death in 1 patient treated with maralixibat (respiratory infection), and was deemed not related to treatment, compared with 0 patients in the placebo group.

Alagille Syndrome (ALGS)

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. Odevixibat (Bylvay) is FDA-approved for the treatment of cholestatic pruritis associated with ALGS in patients 12 months of age and older. Maralixibat (Livmarli) is FDA-approved for the treatment of ALGS in patients 3 months 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 odevixibat (Bylvay) 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. The 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. Odevixibat (Bylvay) and maralixibat (Livmarli) were 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, odevixibat (Bylvay) and maralixibat (Livmarli) should be permanently discontinued if patients progress to portal hypertension or experience a hepatic decompensation event. Additionally, odevixibat (Bylvay) and maralixibat (Livmarli) are 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. The 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. The 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, odevixibat (Bylvay) and maralixibat (Livmarli) are 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 trials evaluating maralixibat (Livmarli) and odevixibat (Bylvay) studied patients with moderate to severe pruritis at baseline. The value of maralixibat (Livmarli) and odevixibat (Bylvay) in patients with mild pruritis has not been established and the drugs 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 two FDA approved agents for pruritis associated with ALGS, which are maralixibat (Livmarli) and odevixibat (Bylvay) at this time; however, there are more 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. Maralixibat (Livmarli) is a newer agent approved for the treatment of ALGS. There is no direct comparative evidence demonstrating superiority of one agent over the other. Trial of all standard of care agents including maralixibat (Livmarli) prior to odevixibat (Bylvay) 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).

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.

XIII. Odevixibat (Bylvay) was studied in one pivotal Phase 3, double-blind, placebo-controlled, trial ASSERT. The pivotal study included 52 pediatric patients (median age: 4.0 years) with ALGS (JAG1 mutation: 92%; NOTCH2 mutation 8%), native liver, elevated serum bile acids (mean: 240 umol/L), and moderate to severe pruritis (mean ObsRO score: 2.9). At baseline, patients were treated with standard of care agents (ursodeoxycholic acid: 89%; other anti-pruritis medication: 98%) that were continued during the trial. Other anti-pruritic drugs included rifampicin, naltrexone, antihistamines, steroids, gabapentin, ondansetron. Patients were excluded if they had prior surgical interruption of the enterohepatic circulation, liver transplantation, and decompensated cirrhosis. The primary endpoint was the least square (LS) mean change from baseline to month six in scratching score as measured by the PRUCISION observer-reported outcome (ObsRO) caregiver instrument. The secondary endpoints were changes from baseline in serum bile acids (sBA) and change from baseline in caregiver-reported sleep parameters. All 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 odevixibat (Bylvay). Safety data is available from 35 patients treated with odevixibat (Bylvay) during the Phase 3 clinical trial ASSERT. Any treatment emergent adverse event rate was 74% in odevixibat (Bylvay) arm compared to 71% in placebo. Drug-related adverse events occurred more frequently in odevixibat (Bylvay) arm compared to placebo (23% vs 18%). Serious adverse events, and drug-related serious adverse events occurred at a similar frequency in both treatment arms. Most common drug related treatment emergent adverse events in the odevixibat (Bylvay) vs placebo arms, respectively, were diarrhea (11% vs 6%), vomiting (6% vs 0%), abdominal pain (3% vs 0%), hepatic enzyme increased (3% vs 1%), INR increased (3% vs 1%), frequent bowel movements (3% vs 0%), hematemesis (3% vs 0%), nausea (3% vs 0%), blood triglyceride increased (3% vs 0%), and weight decreased (3% vs 0%).

Investigational or Not Medically Necessary Uses

I. Odevixibat (Bylvay) and maralixibat (Livmarli) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:

A. 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.

B. Biliary atresia
    i. Odevixibat (Bylvay) is being studied in a Phase 3, double-blind, randomized controlled trial in patients with biliary atresia (NCT04336722). At this time, treatment with odevixibat (Bylvay) remains experimental and investigational.
    ii. Maralixibat (Livmarli) is being studied in a Phase 2, double-blind, randomized controlled trial in patients with biliary atresia (NCT04524390). At this time, treatment with maralixibat (Livmarli) remains experimental and investigational.

C. Primary sclerosing cholangitis (PBC) – maralixibat (Livmarli)
    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. Odevixibat (Bylvay) oral pellets are intended for use by patients weighing less than 19.5 kg and capsules are intended for use by patients weighing 19.5 kg or above.

II. **Odevixibat (Bylvay) Dosing Tables**

A. Table 1: Recommended Dosage for **PFIC** (40mcg/kg/day)

Body weight (kg)	Total Daily Dose (mcg)
7.4 and below	200
7.5 to 12.4	400
12.5 to 17.4	600

17.5 to 25.4	800
25.5 to 35.4	1,200
35.5 to 45.4	1,600
45.5 to 55.4	2,000
55.5 and above	2,400

B. Table 2: Recommended Dosage for **ALGS** (120mcg/kg/day)

Body weight (kg)	Total Daily Dose (mcg)
7.4 and below	600
7.5 to 12.4	1,200
12.5 to 17.4	1,800
17.5 to 25.4	2,400
25.5 to 35.4	3,600
35.5 to 45.4	4,800
45.5 to 55.4	6,000
55.5 and above	7,200

III. **Livmarli (Maralixibat) Dosing Tables**

A. Table 3: Individual Dose Volume by Patient Weight **(ALGS)**

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 (mL)
	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

B. Table 4: Individual Dose Volume by Patient Weight **(PFIC)**

1. The recommended dosage is 570mcg/kg BID. The starting dose is 285mcg/kg QD, and should be increased to 285mcg/kg BID, 428 mcg/kg BID, and then to 570mcg/kg BID, as tolerated. The maximum daily dose should not exceed 38mg (4mL) per day.

Member weight (kg)	285 mcg/kg	428 mcg/kg	570 mcg/kg
	Volume per dose (mL)	Volume per dose (mL)	Volume per dose (mL)
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

References

1. Livmarli. Package insert. Mirum Pharmaceuticals; March 2024.
2. Livmarli product dossier. Mirum Pharmaceuticals; March 2024.
3. Bylvay. Package insert. Ipsen Pharmaceuticals; June 2023.
4. ClinicalTrials.gov. NCT03566238 A double-blind, randomized, placebo-controlled, phase 3 study to demonstrate efficacy and safety of A4250 in children with progressive familial intrahepatic cholestasis types 1 and 2 (PEDFIC 1). June 2018. Available at https://clinicaltrials.gov/ct2/show/NCT03566238. Accessed 9/7/21.
5. ClinicalTrials.gov. NCT03659916 An open-label extension study to evaluate long-term efficacy and safety of A4250 in children with progressive familial intrahepatic cholestasis types 1 and 2 (PEDFIC 2). September 2018. Available at https://clinicaltrials.gov/ct2/show/NCT03659916. Accessed 9/7/21.
6. ClinicalTrials.gov NCT04674761 A Double-blind, randomized, placebo-controlled, Phase 3 study to investigate the efficacy and safety of odevixibat compared to placebo in Patients with Alagille Syndrome. April 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT04674761?term=NCT04674761&draw=2&rank=1. Accessed 5/26/2023.
7. Baumann U., et al. “Effects of odevixibat on pruritus and bile acids in children with cholestatic liver disease: Phase 2 study.” Clinics and research in hepatology and gastroenterology, vol. 45,5 101751. 26 Jun. 2021, doi:10.1016/j.clinre.2021.101751
8. Gunaydin M., et al. “Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment.” Hepatic medicine : evidence and research vol. 10 95-104. 10 Sep. 2018, doi:10.2147/HMER.S137209
9. Düll M., et al. Newer Approaches to the Management of Pruritus in Cholestatic Liver Disease. Curr Hepatology Rep 19, 86–95 (2020). https://doi.org/10.1007/s11901-020-00517-x
10. European Association for the Study of the Liver. “EASL Clinical Practice Guidelines: management of cholestatic liver diseases.” Journal of hepatology vol. 51,2 (2009): 237-67. doi:10.1016/j.jhep.2009.04.009
11. Khurana., et al. “Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials.” Liver international : official journal of the International Association for the Study of the Liver vol. 26,8 (2006): 943-8. doi:10.1111/j.1478-3231.2006.01326.x

12. Thébaut., et al. "Sertraline as an Additional Treatment for Cholestatic Pruritus in Children." Journal of pediatric gastroenterology and nutrition vol. 64,3 (2017): 431-435. doi:10.1097/MPG.0000000000001385
13. Mayo, et al. "Sertraline as a first-line treatment for cholestatic pruritus." Hepatology (Baltimore, Md.) vol. 45,3 (2007): 666-74. doi:10.1002/hep.21553
14. Cies., et al. "Treatment of cholestatic pruritus in children." American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists vol. 64,11 (2007): 1157-62. doi:10.2146/ajhp060453
15. Zellos., et al. Use of oral naltrexone for severe pruritus due to cholestatic liver disease in children. J Pediatr Gastroenterol Nutr. 2010 Dec;51(6):787-9. doi: 10.1097/MPG.0b013e3181eb5ac0. PMID: 20948447.
16. Alagille syndrome Information for Physicians. The Childhood Liver Disease Research Network. Accessed May 26, 2023. https://childrennetwork.org/For-Physicians/Alagille-Syndrome-Information-for-Physicians
17. Alagille syndrome. National Organization for Rare Disease. Updated 2020. Accessed May 26, 2023. https://rarediseases.org/rare-diseases/alagille-syndrome/
18. Kohut TJ, Gilbert MA, Loomes KM. Alagille Syndrome: A Focused Review on Clinical Features, Genetics, and Treatment. Semin Liver Dis. 2021;41(4):525-537. doi:10.1055/s-0041-1730951
19. Kronsten V, Fitzpatrick E, Baker A. Management of cholestatic pruritus in paediatric patients with alagille syndrome: the King's College Hospital experience. J Pediatr Gastroenterol Nutr. 2013;57(2):149-154. doi:10.1097/MPG.0b013e318297e384
20. Yerushalmi B, Sokol RJ, Narkewicz MR, Smith D, Karrer FM. Use of rifampin for severe pruritus in children with chronic cholestasis. J Pediatr Gastroenterol Nutr. 1999;29(4):442-447. doi:10.1097/00005176-199910000-00013
21. Narkewicz MR, Smith D, Gregory C, Lear JL, Osberg I, Sokol RJ. Effect of ursodeoxycholic acid therapy on hepatic function in children with intrahepatic cholestatic liver disease. J Pediatr Gastroenterol Nutr. 1998;26(1):49-55. doi:10.1097/00005176-199801000-00009
22. Mozer-Glassberg Y, Hojsak I, Zevit N, Shapiro R, Shamir R. Pruritus responsive to naltrexone in a patient with cholestatic liver disease. Isr Med Assoc J. 2011;13(2):111-112.
23. Ebhohon E, Chung RT. Systematic review: efficacy of therapies for cholestatic pruritus. Therap Adv Gastroenterol. 2023;16:17562848231172829. Published 2023 May 25. Doi:10.1177/17562848231172829
24. Alagille syndrome Information for Physicians. The Childhood Liver Disease Research Network. Accessed December 16, 2021. https://childrennetwork.org/For-Physicians/Alagille-Syndrome-Information-for-Physicians
25. Alagille syndrome. National Organization for Rare Disease. Updated 2020. Accessed December 16, 2021. https://rarediseases.org/rare-diseases/alagille-syndrome/
26. Shneider, Benjamin L et al. "Placebo-Controlled Randomized Trial of an Intestinal Bile Salt Transport Inhibitor for Pruritus in Alagille Syndrome." Hepatology communications vol. 2,10 1184-1198. 24 Sep. 2018, doi:10.1002/hep4.1244
27. 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;398(10311):1581-1592. doi:10.1016/S0140-6736(21)01256-3
28. Miethke A.G., Moukarzel A., Porta G., et al. Maralixibat in progressive familial intrahepatic cholestasis (MARCH-PFIC): a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lacent Gastroenterol Hepatol*. 2024. Doi: 10.1016/ S2468-1253(24)00080-3

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
New policy titled Ileal Bile Acid Transporter Inhibitors created, combining previous maralixibat (Livmarli) and odevixibat (Bylvay) policies. New indication for maralixibat (Livmarli) added which is in the treatment of PFIC.	06/2024
Maralixibat (Livmarli) has been added as a step requirement for odevixibat (Bylvay) when the request is for ALGS.	11/2023
Original maralixibat (Livmarli) and odevixibat (Bylvay) policies renewal evaluation changed from 12 to six months; added ondansetron as an example of accepted medications in serotonin inhibitor class, updated supportive evidence sections, added related policies sections. New Alagille Syndrome indication added for odevixibat (Bylvay).	07/2023
Original maralixibat (Livmarli) policy created	02/2022
Original odevixibat (Bylvay) policy created	11/2021