Cholestasis Pruritus Prior Authorization Program Summary

POLICY REVIEW CYCLE

Effective Date	Date of Origin
3/1/2023	

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Bylvay™ (odevixibat) Oral Pellet Capsule	Treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: May not be effective in PFIC type 2 patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3)		1
Livmarli™ (maralixibat) Oral solution	Treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 1 year of age and older		

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Progressive Familial Intrahepatic Cholestasis	Progressive familial intrahepatic cholestasis (PFIC) is a rare, hereditary, progressive, and life-threatening liver disorder affecting young children. (5) Impaired production and excretion of bile results in cholestatic liver disease, where biliary substances cannot be eliminated from the liver and thus reenter the circulation, build up in the liver cells, cause elevated bile serum levels and deposition of bilirubin pigments in the tissues as skin, sclerae, mucous membranes and so on (jaundice).(15) Cholestasis can damage the liver, causing cirrhosis and liver failure within the first ten years of life. (7) The three common subtypes of PFIC are PFIC1, PFIC2 and PFIC3. Other subtypes of PFIC have been identified and all present with cholestasis.(5) PFIC1 and PFIC2 onset occurs very early in childhood, early after birth to a young age, and may progress to end stage rapidly, especially PFIC2. PFIC3 typically presents in the first years of childhood with progressive cholestasis, although disease manifestation and cirrhosis in young adulthood has also been described most recently.(7) Patients with PFIC-1 and PFIC-2 have normal GGT levels, while patients with PFIC-3 have increased GGT levels.

	All 3 subtypes of PFIC are caused by defects in bile secretion from hepatocyte to canaliculi and have increased serum bile acid levels. In PFIC-1 and PFIC-2, bile acid secretion is depleted, while in PFIC-3, bile phospholipid secretion is impaired. PFIC-2. PFIC-2 occurs due to a mutation of the major canalicular *BSEP* gene on chromosome 2 (*BSEP/ABCB11*). Expression of this gene is limited to liver. Therefore, although the clinical course of PFIC-2 is similar to that for PFIC-1, extrahepatic manifestations are absent.(15) Cholestatic pruritus is one of the main symptoms of cholestasis in many patients. Pruritus is often out of proportion to the level of jaundice which is often low-grade and can wax and wane. The itching may be very disabling and often does not respond consistently to medications.(5) Chronic pruritus can cause severe sleep deprivation and exhaustion, resulting in fatigue, depression, and even suicidal ideas. Thus, therapy-refractory persistent pruritus can represent an indication for liver transplantation, even in the absence of liver failure.[2] Liver transplantation is generally curative for patients with PFIC1 and PFIC2. However, patients with PFICI may have ongoing disease due to the extrahepatic expression of familial intrahepatic cholestasis type 1 (FIC1).(8) Several possible transmitters and mechanisms have been suggested as possible causes of cholestatic pruritus, including biliary components, endogenous opioids, and the auto-taxin-lysophosphatidic acid (ATX-LPA) axis. However, no definitive correlation between itch intensity and levels of bile salts in serum, urine, or skin has been established to date.(2) No medical therapy of proven benefit for the long-term prognosis of PFIC exists. According to the European Association for the Study of the Liver (EASL) guidelines, ursodiol is the first line medication for cholestasis although it's effect on pruritus varies. Ursodiol has been reported to improve biochemical tests in almost 50% of patients with PFIC3, but generally does not affect PFIC1 and PFIC2.(7) Rifampicin counteracts pruritus by increasing the metabolism of pruritogenic substances, prompting their renal elimination in hydroxylated forms. In addition, the antibacterial effect of rifampicin in the intestine may potentially modify the intestinal metabolism of pruritogenic substances. Because this treatment is well tolerated and its efficacy has been demonstrated, rifampicin is widely considered has the first-line treatment for cholestatic pruritus in children.(9) Oral antihistamines are commonly prescribed to patients with cholestatic pruritus drugs but do not attenuate itching in most cases.(2) The anion exchange resin cholestyramine was initially the only approved medication for cholestatic pruritus, however, its inconsistent efficacy and poor tolerance (nausea, constipation, diarrhea, acidosis) limits its use in children.(9) Bylvay is a systemic, reversible inhibitor of ileal bile acid transporter (IBAT), which decreases the reuptake of bile salts from the terminal ileum into the hepatic portal circulation. The therapy acts locally in the small intestine. The elimination of bile acids from the enterohepatic circulation reduces bile acid levels in serum and the liver. Bylvay may not be effective in PFIC2, a subtype of PFIC with mutations in the ABCB11 gene which causes deficiency of the Bile Salt Export Pump (BSEP) protein.(1) The current European guidelines suggest a stepwise approach to efficiently treat cholestatic pruritus and are listed in order: cholestyramine, rifampicin, Bezafibrate, naltrexone, and sertraline. Sixth line therapy recommendations include the following experimental approaches: gabapentin, phenobarbital, UVB light 1–2×/week, albumin dialysis and nasobiliary drainage.(2)
Alagille Syndrome	Alagille syndrome (ALGS) is a rare genetic disorder that can affect multiple organ systems of the body including the liver, heart, skeleton, eyes and kidneys. Some individuals may have mild forms of the disorder while others may have more serious forms. Most people with Alagille syndrome have mutations in one copy of the *JAG1* gene with 2% of patients affected with 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 in the individual and was not inherited from a parent. The current estimated incidence of ALGS is 1/30,000 –1/45,000.(11) Approximately 90 percent of individuals with Alagille syndrome have a reduced number of bile ducts within the liver. Because of the reduced number of bile ducts, individuals with Alagille syndrome can develop these common symptoms during the first 3 to 4 months of life: cholestasis, pruritus, jaundice, and poor weight gain and growth. 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. In severe cases of Alagille syndrome, liver transplantation may be required. Additional symptoms of ALGS include heart murmurs, congenital heart defects, vertebral differences, thickening of the ring that normally lines the cornea in the eye and distinctive facial features.(11) 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. Livmarli, a reversible inhibitor of the ileal bile acid transporter (IBAT), decreases the reabsorption of bile acids from the terminal ileum improving pruritus in patients with ALGS. Although the complete mechanism by which Livmarli improves pruritus is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts. (10) 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. (11,13)
Efficacy - Bylvay	The efficacy of Bylvay was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial in 62 pediatric patients, aged 6 months to 17 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-function or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal, or who had received a liver transplant were excluded in Trial 1.(1) Patients were randomized to placebo, 40 mcg/kg, or 120 mcg/kg. A total of 13 patients discontinued from trial prematurely either due to no improvement in pruritus (n=11) or due to adverse reactions (n=2). A total of 11 of the 13 patients rolled over to Trial 2 (PEDFIC II) to receive Bylvay 120 mcg/kg/day.(1) Patients treated with Bylvay demonstrated greater improvement in pruritus compared with placebo.(1) Results showed that patients treated with odevixibat achieved a significant decline in itching or scratching and reduced serum bile acid responses. Around 53.5% of patients in the odevixibat arms showed a significant reduction in pruritus, compared to 28.7% in the placebo arm.(6)
Efficacy - Livmarli	The efficacy of Livmarli was assessed in Trial 1, enrolling 31 pediatric (ages 1 to 15, median age 5 years) ALGS patients with JAGGED1 mutation, cholestasis, and pruritus. Patients with surgical interruption of their enterohepatic circulation of bile acid, previous liver transplant, and with decompensated cirrhosis were not enrolled.(14) The study was divided into 6 parts: a 6-week open-label, dose escalation period, a 12-week open-label stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, a 26-week long-term stable dosing period, and a 52-week optional follow-up treatment period, and a long-term optional follow-up treatment period for eligible participants who choose to stay on treatment with Livmarli.(10)

	Patients (90.3%) were administered open-label treatment with Livmarli 380 mcg/kg once daily for 13 weeks after an initial 5-week dose-escalation period; two patients discontinued treatment. The 29 patients who completed the open-label treatment phase were then randomized to continue treatment with Livmarli or placebo during the 4-week drug withdrawal period at Weeks 19-22 (n=16 placebo, n=13 Livmarli). All 29 patients completed the withdrawal period and then received Livmarli at 380 mcg/kg once daily for an additional 26 weeks.(10) Given the patients' young age, an observer-reported outcome was used to measure patients' pruritus symptoms twice daily, each week, on the Itch Reported Outcome Instrument (ItchRO[Obs]). On average, patients administered Livmarli for 22 weeks maintained pruritus reduction whereas those in the placebo group who were withdrawn from Livmarli after Week 18 returned to baseline pruritus scores by Week 22. After re-entering the open-label treatment phase, both randomized treatment groups had similar mean pruritus scores by Week 28, the first week placebo patients received the full dosage of Livmarli after withdrawal. These observer-rated pruritus results are supported by similar results on patient-rated pruritus in patients 5 years of age and older who were able to self-report their itching severity.(10)
Safety	Bylvay and Livmarli do not have any contraindications. (1, 10)

REFERENCES

Number	Reference
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13	National Institute of Diabetes and Digestive and Kidney Diseases. Alagille Syndrome. https://www.niddk.nih.gov/health-information/liver-disease/alagille-syndrome

Number	Reference
14	Safety and Efficacy Study of LUM001 (Maralixibat) With a Drug Withdrawal Period in Participants with Alagille Syndrome (ALGS) (ICONIC). Mirum Pharmaceuticals, Inc. https://clinicaltrials.gov/ct2/show/NCT02160782. Last updated July 2021.
15	Gunaydin M, Bozkurter Cil AT. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. Hepat Med. 2018 Sep 10;10:95-104. doi: 10.2147/HMER.S137209.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Preferred Status	Effective Date
Bylvay ; Bylvay (pellets)	odevixibat cap ; odevixibat pellets cap sprinkle	1200 MCG ; 200 MCG ; 400 MCG ; 600 MCG	M ; N ; O ; Y	N		
Livmarli	maralixibat chloride oral soln	9.5 MG/ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Bylvay ; Bylvay (pellets)	odevixibat cap ; odevixibat pellets cap sprinkle	1200 MCG ; 200 MCG ; 400 MCG ; 600 MCG	Commercial ; HIM ; ResultsRx
Livmarli	maralixibat chloride oral soln	9.5 MG/ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Initial Evaluation

Bylvay (odevixibat) will be approved when ALL of the following are met:

1. ONE of the following:
   - A. The patient has a diagnosis of progressive familial intrahepatic cholestasis (PFIC) with pruritus (medical records required) AND BOTH of the following:
     1. The patient is 3 months of age or older **AND**
     2. The patient is starting therapy with the requested agent or has already begun therapy as a pediatric patient **OR**
   - B. The patient has another FDA approved indication for the requested agent and route of administration **OR**
   - C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND**
2. ONE of the following:
   - A. The patient has tried and had an inadequate response to a standard cholestasis pruritus treatment agent (i.e., ursodiol, cholestyramine, or rifampicin) **OR**
   - B. The patient has an intolerance or hypersensitivity to therapy with a standard cholestasis pruritus treatment agent (i.e., ursodiol, cholestyramine, or rifampicin) **OR**
   - C. The patient has an FDA labeled contraindication to ALL standard cholestasis pruritus treatment agents (i.e., ursodiol, cholestyramine, and rifampicin) **AND**
3. The patient does NOT have a diagnosis of PFIC2 with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3) **AND**
4. The patient's INR is less than 1.4 **AND**
5. The patient has an ALT and total bilirubin that is less than 10-times the upper limit of normal (ULN) **AND**
6. ONE of the following:
   - A. The patient has NOT had a liver transplant **OR**
   - B. The patient has had a liver transplant and the prescriber has provided information in support of using the requested agent post liver transplant **AND**
7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
8. The patient will NOT be using the requested agent in combination with another Ileal Bile Acid Transport (IBAT) inhibitor agent (e.g., Livmarli) **AND**

Module	Clinical Criteria for Approval
	9. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months **Livmarli (maralixibat)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of Alagille syndrome with pruritus (medical records required) B. The patient has another FDA approved indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the required indication 3. ONE of the following: A. The patient has tried and had an inadequate response to a standard cholestasis pruritus treatment agent (i.e., ursodiol, cholestyramine, naltrexone, or rifampicin) **OR** B. The patient has an intolerance or hypersensitivity to therapy with a standard cholestasis pruritus treatment agent (i.e., ursodiol, cholestyramine, naltrexone, or rifampicin) **OR** C. The patient has an FDA labeled contraindication to ALL standard cholestasis pruritus treatment agents (i.e., ursodiol, cholestyramine, naltrexone, and rifampicin) **AND** 4. The patient does NOT have decompensated cirrhosis **AND** 5. That patient has NOT had surgical interruption of the enterohepatic circulation of bile acid **AND** 6. ONE of the following: A. The patient has NOT had a liver transplant **OR** B. The patient has had a liver transplant and the prescriber has provided information in support of using the requested agent post liver transplant **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The patient will NOT be using the requested agent in combination with another Ileal Bile Acid Transport (IBAT) inhibitor agent (e.g., Bylvay) **AND** 9. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another Ileal Bile Acid Transport (IBAT) inhibitor agent (e.g., Bylvay, Livmarli) **AND**

Module	Clinical Criteria for Approval
	5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

