09-J4000-09

Original Effective Date: 01/01/22

Reviewed: 09/11/24

Revised: 10/15/24

Subject: Odevixibat (Bylvay™) Capsule

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Odevixibat (Bylvay) in an oral therapy initially approved by the U.S. Food and Drug Administration (FDA) in July 2021 for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis. In June 2023, the FDA approved an additional indication for the treatment of cholestatic pruritus in patients 12 months of age and older with Alagille Syndrome (ALGS). Maralixibat (Livmarli) oral solution was previously approved for this same indication of ALGS in September 2021. Odevixibat is a non-systemic, reversible inhibitor of the ileal bile acid transporter (IBAT) that decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum. Progressive familial intrahepatic cholestasis (PFIC) is an ultra-rare, heterogeneous group of liver disorders of autosomal recessive inheritance that disrupt bile formation and are characterized by an early onset of cholestasis with pruritus and malabsorption, which rapidly progresses, eventually leading to liver failure. Most patients with PFIC require biliary diversion surgery or liver transplant by 30 years of age or earlier. The suspected incidence of PFIC is between 1 in 50,000 and 1 in 100,000 births and an estimated 600 children in the United States are afflicted. While PFIC types 1, 2, and 3 are the most common, new subtypes are still being discovered. Each subtype is uniquely categorized based on the mutated gene and resultant protein deficiency. For example, PFIC1 is due to a mutation in the *ATP8B1* gene that encodes the FIC1 (familial intrahepatic cholestasis 1) protein, and PFIC2 is due to a mutation in the *ABCB11* gene that encodes the BSEP (bile salt export pump). Each subtype has a unique clinical presentation, management strategies, and outcomes. Initial care for patients with PFIC addresses nutritional problems, including supplementation with and monitoring of fat-soluble vitamins. However, the most prominent and problematic manifestation of PFIC (in particular in types 1 and 2) is pruritis, which can lead to physical abrasions and scarring, as well as functional impacts (e.g., sleep and mood disorders) and deterioration in overall quality of life. Therapy-refractory persistent pruritus can be an indication for liver transplantation, even in the absence of liver failure. Liver transplantation is generally

curative for patients with PFIC 1 and 2; however, patients with PFIC1 may have ongoing disease due to the extrahepatic expression of the FIC1 protein.

Odevixibat was the first pharmacologic therapy specifically approved for this PFIC. A second IBAT inhibitor, maralixibat (Livmarli), was approved for PFIC in March 2024. Before IBAT inhibitor therapy, treatment relied on supportive pharmacologic therapy for symptomatic relief (e.g., ursodiol, rifampicin, cholestyramine, antihistamines) or surgical intervention (e.g., surgical biliary diversion, liver transplantation). 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 often does not affect PFIC1 and PFIC2. 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 a first-line treatment for cholestatic pruritus in children. The anion exchange resin cholestyramine was initially the only approved medication for cholestatic pruritus; however, its inconsistent efficacy and poor tolerance (nausea, constipation, diarrhea) often limits its use in children.

The safety and efficacy of odevixibat leading to FDA approval for PFIC was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial (NCT03566238; aka, Trial 1 in the product labeling). Trial 1 was conducted 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 (ULN), or who had received a liver transplant were excluded. Patients were randomized to placebo (n=20), 40 mcg/kg (n=23), or 120 mcg/kg (n=19). Study drug was administered once daily with a meal in the morning. In patients weighing less than 19.5 kg or patients who could not swallow the whole capsule, study drug was sprinkled on soft food and then administered orally. Given the patients' young age, a single-item observer-reported outcome (ObsRO) was used to measure patients' scratching as observed by their caregiver twice daily (once in the morning and once in the evening). Scratching was assessed on a 5-point ordinal response scale, with scores ranging from 0 (no scratching) to 4 (worst possible scratching). Patients were included if the average scratching score was greater than or equal to 2 (medium scratching) in the 2 weeks prior to baseline. The median age (range) of the patients was 3.2 (0.5 to 15.9) years; only 3 patients were older than 12 years of age. Of the 62 patients, 50% were male and 84% were white; 27% had PFIC1, and 73% had PFIC2. The majority of patients were being treated with ursodiol (81%) and rifampicin (66%) at baseline. The mean (standard error) scratching score in the 2 weeks prior to baseline was 2.9 (0.08). A total of 13 patients discontinued from the trial prematurely either due to no improvement in pruritus (n=11) or due to adverse reactions (n=2); 5/20 (25%) patients discontinued from the placebo arm and 8/42 (19%) patients discontinued from the odevixibat arms. A total of 11 of the 13 patients rolled over to an extension trial (Trial 2) to receive odevixibat 120 mcg/kg/day. One patient treated with odevixibat 120 mcg/kg/day withdrew from the trial due to a treatment-emergent adverse event of diarrhea.

The Table below presents the results of the comparison between odevixibat and placebo on the mean of patients' percentage of ObsRO assessments over the 24-week treatment period that were scored as 0

(no scratching) or 1 (a little scratching). Patients treated with odevixibat demonstrated greater improvement in pruritus compared with placebo.

	Placebo (n=20)	**Odevixibat 40 mcg/kg/day (n=23)**	**Odevixibat 120 mcg/kg/day (n=19)**
Mean* Percentage of Assessments Over the Treatment Period Scored as 0 (No Scratching) or 1 (A Little Scratching)			
Mean (SE)	13.2% (8.7)	35.4% (8.1)	30.1% (9)
Mean Difference vs Placebo (95% CI)		22.2% (4.7, 39.6)	16.9% (-2.0, 35.7)

*Based on least squares means from analysis of covariance model with daytime and nighttime baseline pruritus scores as covariates and treatment group and stratification factors (i.e., PFIC type and age category) as fixed effects.

Alagille syndrome is a rare, autosomal dominant genetic disorder that can affect multiple organ systems, including the liver, heart, skeleton, eyes, and kidneys. Most patients have mutations in one copy of the JAG1 gene, but a small percentage (2%) have mutations of the NOTCH2 gene. The estimated incidence of ALGS is approximately 1/30,000 to 1/45,000. The specific symptoms and severity of ALGS can vary greatly from one person to another. Approximately 90% of individuals with ALGS have a reduced number of bile ducts (bile duct paucity) that can progress to liver disease. Patients may present in the first 3 months of life with cholestasis, jaundice, poor weight gain and growth, and pruritus. Many individuals with ALGS also have heart abnormalities that can range from benign heart murmurs to serious structural defects. Individuals usually have distinctive facial features including deeply set and widely spaced (hypertelorism) eyes, a pointed chin, and broad forehead. One of the more problematic manifestations of ALGS is pruritus, which can lead to physical abrasions and scarring, as well as functional impacts (e.g., sleep and mood disorders) and deterioration in quality of life.

Odevixibat is the second pharmacologic therapy specifically approved for ALGS. The first being the IBAT inhibitor, maralixibat (Livmarli). Prior to IBAT inhibitor therapy, treatment relied on supportive pharmacologic therapy for symptomatic relief (e.g., ursodiol, rifampicin, cholestyramine, antihistamines) or surgical intervention (e.g., surgical biliary diversion, liver transplantation). According to the European Association for the Study of the Liver (EASL) guidelines, ursodiol is often a first-line medication for cholestasis although it's effect on pruritus varies, and the guidelines note that for ALGS specifically no effective medical treatment is known (prior to IBAT). 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 a first-line treatment for cholestatic pruritus in children. The anion exchange resin cholestyramine was initially the only approved medication for cholestatic pruritus; however, its inconsistent efficacy and poor tolerance (nausea, constipation, diarrhea) often limits its use in children.

The safety and efficacy of odevixibat leading to FDA approval for ALGS was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial (NCT04674761; aka, Trial 3 in the product labeling).

Trial 3 was conducted in 52 pediatric patients, aged 6 months to 15 years, with a confirmed diagnosis of ALGS and presence of pruritus at baseline. Patients who had decompensated liver disease, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT was greater than 10-times the upper limit of normal (ULN) at screening, whose total bilirubin was greater than 15-times the ULN at screening, or who had received a liver transplant were excluded. Patients were randomized to placebo (n=17) or 120 mcg/kg (n=35). Study drug was administered once daily with a meal in the morning. In patients weighing less than 19.5 kg or patients who could not swallow the whole capsule, study drug was sprinkled on soft food and then administered orally. Median age (range) of the patients was 6.1 (1.7 to 15.5) years in the odevixibat group and 4.2 (0.5 to 14.3) years in the placebo group; 5 patients were older than 12 years of age. Of the 52 patients, 52% were male and 83% were white; 92% of patients had the JAG1 mutation and 8% had the NOTCH2 mutation. The mean (standard deviation [SD]) scratching score in the 2 weeks prior to baseline was 2.9 (0.6). Baseline mean (SD) eGFR was 159 (51.4) mL/min/1.73 m^2. Baseline median (range) ALT, AST, and total bilirubin were 152 (39 to 403) U/L, 135 (57 to 427) U/L, and 2.0 (0.4 to 1.4) mg/dL, respectively. Given the patients' young ages, the same ObsRO as used in Trial 1 for PFIC was used to measure patients' scratching severity. The patients treated with odevixibat demonstrated greater improvement in pruritus compared with placebo. At 6 months the placebo groups average scratching score reduced from a baseline of 3 to 2.2 (difference of 0.8), while the odevixibat groups average score reduced from a baseline of 2.8 to 1.1 (difference of 1.7). This resulted in a mean difference vs. placebo of -0.9 (95% CI, -1.4, -0.3; p=0.002).

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of odevixibat (Bylvay) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "11"):

1. Member has a confirmed diagnosis of **EITHER** of the following ("a" or "b"):
    a. Progressive familial intrahepatic cholestasis (PFIC) as evidenced by **BOTH** of the following ("i" and "ii"):
        i. Genetic testing demonstrating a gene mutation affiliated with progressive familial intrahepatic cholestasis (for example, mutations in *ATP8B1*, *ABCB11*, *ABCB4*, *TJP2*, *NR1H4*, or *Myo5b* genes) – *medical record documentation of the member's genetic testing results must be submitted*
        ii. A pretreatment (baseline) total serum bile acid concentration above the upper limit of normal (ULN) for the member's age [according to the reporting laboratory] - *medical record documentation of the member's baseline total serum bile acid level must be submitted*
    b. Alagille syndrome (ALGS) with cholestasis as evidenced by **BOTH** of the following ("i" and "ii"):

i. Genetic testing demonstrating a mutation in the JAG1 or NOTCH2 genes* – medical record documentation of the member's genetic testing results must be submitted

*Very rarely a patient may have ALGS with no identifiable gene mutation. In these cases, the specialist physician must provide medical record documentation detailing how the member's clinical work-up, signs and symptoms of disease, and differential diagnosis (i.e., exclusion of other causes) has confirmed the member has ALGS.

ii. A pretreatment (baseline) total serum bile acid concentration above the upper limit of normal (ULN) for the member's age [according to the reporting laboratory] - *medical record documentation of the member's baseline total serum bile acid level must be submitted*

2. Member 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)
3. Member has a history of moderate-to-severe pruritus due to cholestasis associated with ALGS or PFIC – *medical records documenting the member's severity of pruritis, and scratching must be submitted*
4. Member has **NOT** previously received a liver transplant
5. Member does **NOT** have clinical evidence of decompensated cirrhosis
6. **ANY** of the following regarding ursodiol treatment ("a", "b", or "c"):
   a. Member is currently being treated with ursodiol
   b. Member has had a previous trial of ursodiol treatment with minimal clinical benefit
   c. Member had intolerable adverse effects with or has a contraindication to treatment with ursodiol - *the specific intolerance or contraindication must be provided*
7. Member has tried and had an inadequate response to at least **ONE** other systemic cholestasis pruritus treatment [cholestyramine, naltrexone, rifampin, or sertraline], **OR** the member has intolerances and/or contraindications to **ALL** of these medications – *if applicable the specific intolerances and/or contraindications must be provided*
8. Odevixibat will **NOT** be used in combination with another ileal bile acid transporter (IBAT) inhibitor [for example, maralixibat (Livmarli)]
9. Odevixibat is prescribed by, or in consultation with, a gastroenterologist, hepatologist, or other physician who specializes in the management of ALGS or PFIC
10. Member is at least 3 months of age or older
11. Dosage of odevixibat does not exceed 120 mcg/kg body weight (up to a maximum of 6 mg for PFIC, or 7.2 mg for ALGS) daily, rounded down to the closest 200 mg interval [daily maximums for PFIC: 200 mcg oral pellet - 30, 400 mcg capsule - 15, 600 mcg oral pellet - 10, and 1200 mcg capsule – 5; daily maximums for ALGS: 200 mcg oral pellet - 36, 400 mcg capsule - 18, 600 mcg oral pellet –12, and 1200 mcg capsule – 6].

Approval duration: 6 months

Continuation of odevixibat (Bylvay) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7"):

1. An authorization or reauthorization for odevixibat has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of ALGS or PFIC (if another health plan, documentation of a health plan-paid claim for odevixibat during the 90 days immediately before the authorization request must be submitted); **OR** the member has previously met **ALL** indication-specific criteria
2. Member has had a beneficial response to therapy as determined by a clinically meaningful reduction in pruritis – *medical record documentation citing the impact of treatment on the member's pruritis must be submitted*
3. Member has **NOT** received a liver transplant
4. Member does **NOT** have clinical evidence of decompensated cirrhosis
5. Odevixibat will **NOT** be used in combination with another ileal bile acid transporter (IBAT) inhibitor [for example, maralixibat (Livmarli)]
6. Odevixibat is prescribed by, or in consultation with, a gastroenterologist, hepatologist, or other physician who specializes in the management of ALGS or PFIC
7. Dosage of odevixibat does not exceed 120 mcg/kg body weight (up to a maximum of 6 mg for PFIC, or 7.2 mg for ALGS) daily, rounded down to the closest 200 mg interval [daily maximums for PFIC: 200 mcg oral pellet - 30, 400 mcg capsule - 15, 600 mcg oral pellet - 10, and 1200 mcg capsule – 5; daily maximums for ALGS: 200 mcg oral pellet - 36, 400 mcg capsule - 18, 600 mcg oral pellet – 12, and 1200 mcg capsule – 6].

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC)
    - Limitations of Use: May not be effective in a subgroup of PFIC type 2 patients with specific ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3)
    - The recommended dosage for PFIC is 40 mcg/kg once daily in the morning with a meal. If there is no improvement in pruritus after 3 months, the dosage may be increased in 40 mcg/kg increments up to 120 mcg/kg once daily not to exceed a total daily dose of 6 mg.
- Indicated for the treatment of cholestatic pruritus in patients 12 months of age and older with Alagille Syndrome (ALGS)
    - The recommended dosage for ALGS is 120 mcg/kg once daily in the morning with a meal, but not to exceed a total daily dose of 7.2 mg. Dose reduction to 40 mcg/kg/day may be considered

if tolerability issues occur in the absence of other causes. Once tolerability issues stabilize, increase to 120 mcg/kg/day.

- Odevixibat is available as both oral pellets and capsules. For the pellets, mix the contents of the shell containing oral pellet(s) into soft food. Do NOT mix in liquids, and do NOT swallow the shell containing oral pellets whole. Patients who are exclusively on liquid food should not use the oral pellets. Refer to the product labeling for additional instructions.
- Per the product labeling, the oral pellets are intended for use by patients weighing less than 19.5 kg and the capsules for patients weighing 19.5 kg or above.

Dose Adjustments

- **Hepatic Impairment:** Establish the baseline pattern of variability of liver tests prior to starting odevixibat, so that potential signs of liver injury can be identified. Monitor liver tests (e.g., ALT [alanine aminotransferase], AST [aspartate aminotransferase], TB [total bilirubin], DB [direct bilirubin] and International Normalized Ratio [INR]) during treatment. Interrupt treatment if new onset hepatic function abnormalities occur or symptoms consistent with clinical hepatitis are observed. Once the liver test abnormalities either return to baseline values or stabilizes at a new baseline value, consider restarting odevixibat at the recommended dosage. Consider discontinuing permanently if liver test abnormalities recur. Permanently discontinue treatment if a patient experiences a hepatic decompensation event (e.g., variceal hemorrhage, ascites, hepatic encephalopathy)
- **Renal Impairment:** Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- 200 mcg and 600 mcg oral pellets [bottles of 30]
- 400 mcg and 1200 mcg capsules [bottles of 30]
- Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F)

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Liver Test Abnormalities**: Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be required if abnormalities occur. For persistent or recurrent liver test abnormalities, consider treatment discontinuation.
- **Diarrhea**: Treat dehydration. Treatment interruption or discontinuation may be required for persistent diarrhea.

- **Fat-Soluble Vitamin (FSV) Deficiency**: Obtain baseline levels and monitor during treatment. Supplement if deficiency is observed. If FSV deficiency persists or worsens despite FSV supplementation, discontinue treatment.
- **Bile Acid Binding Resins**: Bile acid binding resins may bind odevixibat in the gut, which may reduce efficacy. Administer bile acid binding resins (e.g., cholestyramine, colesevelam, or colestipol) at least 4 hours before or 4 hours after administration of odevixibat.

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, nos

ICD-10 Diagnosis Codes That Support Medical Necessity

E78.7	Disorder of bile acid and cholesterol metabolism, unspecified
K76.8	Other specified diseases of liver
L29.81	Cholestatic pruritus
Q44.71	Alagille syndrome
Q44.79	Other congenital malformations of liver

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

Maralixibat (Livmarli) Capsule, 09-J4000-10

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/11/24.

GUIDELINE UPDATE INFORMATION:

01/01/22	New Medical Coverage Guideline.

10/15/22	Review and revision to guidelines consisting of updates to the Position Statement.
10/15/23	Review and revision to guidelines consisting of updates to the description, position statement, dosage/administration, billing/coding, and reference based on the new Alagille Syndrome indication.
10/15/24	Review and revision to guidelines consisting of updates to the description, position statement, billing/coding, and references.