Original Effective Date: 11/01/2021
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Last P&T Approval/Version: 01/25/2023
Next Review Due By: 01/2024
Policy Number: C22109-A

Bylvay (odevixibat)

PRODUCTS AFFECTED

Bylvay (odevixibat)

COVERAGE POLICY

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

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

DIAGNOSIS:
Progressive familial intrahepatic cholestasis (PFIC)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

A. PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPE 1 AND 2
   1. Documented diagnosis of progressive familial intrahepatic cholestasis (PFIC), including documented molecular genetic confirmation of PFIC-1 or PFIC-2
      AND
   2. Documentation member does not have a pathologic variation of the ABCB11 gene that

predicts complete absence of the bile salt export pump (BSEP) protein [DOCUMENTATION REQUIRED]
AND
3. Prescriber attests to obtaining baseline liver tests, fat-soluble vitamin levels, and hydration status, and monitoring during treatment as recommended per FDA label
AND
4. Documentation member has the presence of pruritus
AND
5. Prescriber attests that drug-induced pruritus has been ruled out
AND
6. Documentation of member's current weight (within the last 30 days)
AND
7. Prescriber attests that member does not have ANY of the following: history of liver transplant, history of biliary diversion surgery within the past 6 months or clinical evidence of decompensated cirrhosis
AND
8. Documentation member is: (a) concurrently using ursodiol OR (b) has tried and failed (1 month at 20- 30mg/kg/day) of ursodiol OR (c) has an FDA labeled contraindication to ursodiol

CONTINUATION OF THERAPY:

A. PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPE 1 AND 2
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms
AND
4. Prescriber attests to continued monitoring of liver tests, fat-soluble vitamin levels, and hydration status during treatment as recommended per FDA label
AND
5. Documentation of member's current weight (within the last 30 days)

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 12 months

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

AGE RESTRICTIONS:
3 months of age and older

QUANTITY:
40 mcg/kg once daily
30 days of therapy per dispense
NOTE: oral pellets are intended for use by patients weighing less than 19.5 kilograms, capsules are intended for use by patients weighing 19.5 kilograms or above

Maximum Quantity Limits – 40 mcg/kg once daily for 3 months, after 3 months the dose 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.

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

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Ileal Bile Acid Transporter (IBAT) Inhibitors

FDA-APPROVED USES:
Bylvay (odevixibat) is indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC).
Limitation of Use: BYLVAY 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).

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of liver disorders of autosomal recessive inheritance, presenting as intrahepatic cholestasis in infancy or early childhood and resulting in end stage liver disease (ESLD) and death or liver transplantation in infancy to adulthood. The disease has been classified into three types (types 1, 2 and 3) based on the genetic defect involved in bile transport. All the three types of PFIC are caused by defects in bile secretion from hepatocyte to canaliculi. The defects are in form of penetrant mutations in genes encoding proteins associated with hepatocellular transport system
PFIC is typically diagnosed using liver function tests (e.g., gamma-glutamyl transferase [GGT], aspartate aminotransferase [AST], alanine transaminase [ALT]), bile acid tests, liver biopsy, and genetic testing. While PFIC types 1–3 are the most common, new types are still being discovered. In types 1–3, benign recurrent intrahepatic cholestasis (BRIC), a transient presentation of PFIC, has occurred.
PFIC accounts for 10–15% cases of neonatal cholestasis syndrome2,3 and 10–15% of children requiring liver transplantation. It is a rare disease with an estimated incidence of 1 per 50,000 to 1 per 100,000 births although the exact prevalence is not known. The disease affects both genders equally and has been reported from around the world. Patients typically develop fibrosis and end-stage liver disease before adulthood, which can be fatal if untreated. Most patients with PFIC require biliary diversion surgery or liver transplant by 30 years of age.
Treatment-
Medical therapy is the first line of treatment in patients with all types of PFIC. The objectives are to provide relief from pruritus, improve the nutritional status, correct vitamin deficiencies and treat complications of advanced liver disease like ascites and variceal bleeding if present. Simple measures like keeping the skin moisturized and trimming the fingernails are helpful to provide symptomatic relief. The total caloric intake

should be around 125% of the recommended daily allowance (RDA). Dietary fat should be provided largely as medium chain triglycerides (MCT oil) as they do not require bile salts for absorption and help in improving nutrition. Water soluble vitamins are given at 1–2 times of the age-appropriate RDA. The fat soluble vitamins are usually supplemented in the following dosage in children: vitamin A—5000–25,000 IU/day PO, vitamin D 400–800 IU/day PO, vitamin E 50–100 IU/day PO and vitamin K 2.5–5 mg/day PO or 2–5 mg intravenous every 3–4 weeks. Adequate sunlight exposure and dietary intake of calcium (800–2000 mg/day PO) is also essential. It is important to evaluate the child both clinically as well as biochemically (serum levels of vitamins) for signs of specific vitamin deficiencies and adjust the supplements accordingly.
The most commonly used drug for pruritus is ursodeoxycholic acid (Ursodiol) which is a hydrophilic bile acid, non-toxic to hepatocytes.
Ursodeoxycholic acid (Ursodiol) is a safe drug with no major side effects and has been shown to be effective in all forms of PFIC. Patients with total defect in MDR3 gene expression are usually nonresponders to ursodeoxycholic acid (Ursodiol) therapy.
Overall, complete or partial response is seen in approximately 35–40% of low GGT PFIC and 70% cases of high GGT PFIC.

Ileal bile acid reabsorption transporters were not included in the 2018 Hepatology guidelines as these agents were still investigational at the time of publication.

Surgical Management

Nasobiliary drainage

Nasobiliary drainage involves inserting a tube into the nose that reaches the bile ducts to drain them. This temporarily relieves itching and may predict the patient's response to biliary diversion.

Partial external biliary diversion (PEBD)

PEBD entails attaching a portion of the intestine between the gallbladder and an ostomy, which allows bile acids to drain externally. By stopping some bile acids from re-entering the intestine and passing into the liver, patients may experience a reduction in pruritus. Partial internal biliary diversion and ileal exclusion are procedures that do not require an ostomy but have fewer data support in their use.

Liver transplant

A liver transplant is reserved for severe cases in which patients have advanced cirrhosis, live failure, or liver cancer, or are unresponsive to other interventions. It may worsen or fail to improve extrahepatic manifestations, such as diarrhea, liver steatosis, and short stature, particularly I patients with PFIC type 1.

Common Types of PFIC

Common Name	Protein Deficiency	Mutated Gene	Clinical Presentation	Clinical Outcomes and Management
PFIC1	FIC1	ATP8B1	• Intense pruritus • Extrahepatic symptoms • Diarrhea • Sometimes pancreatitis • Sometimes cough, wheezing • Sometimes hearing loss • Sometimes stunted growth • Normal GGT cholestasis	• Moderate progression • May progress to cirrhosis and end stage liver disease, most often in the second or third decade of life • Can develop posttransplant hepatic steatosis and diarrhea • Extrahepatic symptoms may develop or worsen post- transplant

PFIC 2	BSEP	ABCB11	• Intense pruritus • Potential to develop hepatocellular carcinoma and cholangiocarcinoma • Gallstones • Normal GGT cholestasis	• Moderate to rapid progression • Biliary diversion surgery success can be dependent on the genetic defect • Liver transplant may lead to • antibody-induced BSEP deficiency, which may lead to disease recurrence
PFIC 3	MDR3	ABCB4	• Mild to moderate pruritus • Reduced bone density • Potential to develop hepatocellular carcinoma and cholangiocarcinoma • Gallstones • Elevated GGT cholestasis	• Extremely variable progression • Patients with MDR3 expression have better responses to ursodiol • Biliary diversion may not work as well compared to other types • Liver transplant is curative

Bylvay (odevixibat) is indicated for the treatment of pruritus in patients 3 months of age and older with PFIC. Bylvay may not be effective in PFIC type 2 patients with ABCB11 variants, which result in defects or absence of bile salt export pump protein (BSEP-3).

Bylvay reversibly inhibits the ileal bile acid transporter (IBAT). By doing so, it decreases reabsorption of bile acids from the terminal ileum of the intestine. The mechanism of action by which Bylvay treats pruritus in patients with PFIC is unknown; however, it is hypothesized that the mechanism involves IBAT inhibition, which causes decreased reuptake of bile salts, as evidenced by a decrease in serum bile acids in patients taking Bylvay.

Bylvay may not be effective in PFIC type 2 patients with ABCB11 variants, which result in defects or absence of bile salt export pump protein (BSEP-3). The BSEP-3 protein works as a pump that moves bile salts out of the liver. Deficiency of this protein directly leads to buildup of bile in liver cells, thereby damaging the liver.

Patients with BSEP-3 deficiency were excluded from Bylvay's clinical trials, as they were unlikely to respond to therapy.

The efficacy of BYLVAY was evaluated in Trial 1 (NCT03566238), a 24-week, randomized, double-blind, placebo-controlled trial. 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 in Trial 1.

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.

Median age (range) of the patients in Trial 1 was 3.2 (0.5 to 15.9) years; 3 patients were older than 12 years of age. Of the 62 patients, 50% were male and 84% were white; 27% had PFIC type 1, and 73% had PFIC type 2. The mean (standard error [SE]) scratching score in the 2 weeks prior to baseline was 2.9 (0.08). Baseline mean (SE) eGFR was 164 (30.6) mL/min/1.73 m2. Baseline median (range) ALT, AST, and total bilirubin were 65 (16-798) U/L, 83.5 (32-405) U/L, and 2.2 (0.2-18.6) mg/dL, respectively.

In Trial 1, 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); 5/20 (25%) patients discontinued from the placebo arm

and 8/42 (19%) patients discontinued from the BYLVAY arms. A total of 11 of the 13 patients rolled over to Trial 2 to receive BYLVAY 120 mcg/kg/day. One patient treated with BYLVAY 120 mcg/kg/day withdrew from the trial due to a treatment-emergent adverse event of diarrhea.

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 in Trial 1 if the average scratching score was greater than or equal to 2 (medium scratching) in the 2 weeks prior to baseline.

The table below presents the results of the comparison between BYLVAY 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 BYLVAY demonstrated greater improvement in pruritus compared with placebo. Figure 1 displays the mean of patients' worst weekly average scratching scores in each treatment group for each month, where the weekly average utilized the worst score from each day (morning or evening score).

	Placebo (n=20)	BYLVAY 40 mcg/kg/day (n=23)	BYLVAY 120 mcg/kg/day (n=19)
Mean[a] 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 (9.0)
Mean Difference vs Placebo (95% CI)		22.2 (4.7, 39.6)	16.9 (-2.0, 35.7)

[a] 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.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

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

OTHER SPECIAL CONSIDERATIONS:

Administration

- Capsules for oral administration should not be crushed or chewed
- Capsules for oral administration may be swallowed whole OR the contents of the capsule may be sprinkled into soft food or mixed with liquid.
- Shell containing oral pellets should be opened and mixed into soft food or liquid; shell should be discarded
- Do not swallow the 200 mcg or 600 mcg capsule(s) containing Oral Pellets whole. These are intended to be opened and the contents mixed into soft food. Take BYLVAY in the morning with a meal.
- Follow stepwise administration Instructions for Oral Pellets and Capsules for patients unable to swallow the capsules whole.
- For patients taking bile acid binding resins, take BYLVAY at least 4 hours before or 4 hours after taking a bile acid binding resin

CODING/BILLING INFORMATION

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

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Bylvay CAPS 400MCG
Bylvay CAPS 1200MCG
Bylvay (Pellets) CPSP 200MCG
Bylvay (Pellets) CPSP 600MCG

REFERENCES

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3. Jacquemin, E. (2012). Progressive familial intrahepatic cholestasis. Clinics And Research In Hepatology And Gastroenterology, 36, S26-S35. doi: 10.1016/s2210-7401(12)70018-9
4. Srivastava, A. (2014). Progressive Familial Intrahepatic Cholestasis. Journal Of Clinical And Experimental Hepatology, 4(1), 25-36. doi: 10.1016/j.jceh.2013.10.005
5. This Study Will Investigate the Efficacy and Safety of A4250 in Children With PFIC Types 1 or 2 - Full Text View - ClinicalTrials.gov. (2021). Retrieved 9 September 2021, from

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms	Q1 2023
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy References	Quarter 3 2022
Q2 2022 Established tracking in new format	Historical changes on file