Original Effective Date: 11/01/2021
Current Effective Date: 04/11/2025
Last P&T Approval/Version: 01/29/2025
Next Review Due By: 01/2026
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), Cholestatic pruritus in patients with Alagille syndrome (ALGS)

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. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

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. Prescriber attests, or the clinical reviewer has found, that the 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
7. 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

B. CHOLESTATIC PRURITUS WITH ALAGILLE SYNDROME:
1. Documented diagnosis of Alagille syndrome
AND
2. Documentation of ONE of the following that support the diagnosis [DOCUMENTATION REQUIRED]:
   a) Clinical features with involvement in 3 of 7 main organ systems (hepatic, ocular, skeletal, vascular, facial, cardiac, or renal) OR
   b) Liver biopsy showing bile duct paucity OR
   c) Use of an approved genetic test showing mutation/deletion of 1 of 2 known genes (JAG1, NOTCH2)
   AND
3. Documentation of member's symptoms of moderate to very severe pruritus
AND
4. Prescriber attests to obtaining baseline liver tests, fat-soluble vitamin levels, and hydration status, and monitoring during treatment as recommended per FDA label
AND
5. Prescriber attests, or the clinical reviewer has found, that member does not have history of liver transplant, or clinical evidence of decompensated cirrhosis
AND
6. IF THIS IS A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary alternatives for the given diagnosis (see BACKGROUND). Documentation of medication(s) tried, dates of trial(s) and reason for treatment failure(s) is required.

CONTINUATION OF THERAPY:

A. PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPE 1 AND 2, CHOLESTATIC PRURITUS WITH ALAGILLE SYNDROME:
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

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:
PFIC: 3 months of age and older
ALGS: 12 months of age and older

QUANTITY:
PFIC: 40 mcg/kg once daily
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. 30 days of therapy per dispense.

ALGS: 120mcg/kg once daily

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.

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:
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 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).

Indicated for the treatment of cholestatic pruritus in patients 12 months of age and older with Alagille syndrome (ALGS).

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Progressive familial intrahepatic cholestasis (PFIC)

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)	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.

Alagille syndrome (ALGS)

Alagille syndrome (ALGS) is a rare autosomal dominant genetic disorder caused by pathogenic variants in JAG1 or NOTCH2, which encode fundamental components of the Notch signaling pathway. The specific symptoms and severity of Alagille syndrome can vary greatly from one person to another, even within the same family. Clinical features span multiple organ systems including hepatic, cardiac, vascular, renal, skeletal, craniofacial, and ocular, and occur with variable phenotypic penetrance. Common symptoms, which often develop during the first three months of life, include blockage of the flow of bile from the liver (cholestasis), yellowing of the skin and mucous membranes (jaundice), poor weight gain and growth, and severe itching (pruritus).
Additional symptoms include heart murmurs, congenital heart defects, vertebral (back bone) differences, thickening of the ring that normally lines the cornea in the eye (posterior embryotoxon) and distinctive facial features. Most people with Alagille syndrome have changes (mutations) in one copy of the JAG1 gene. A small percentage (2 percent) of patients has 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 ("de novo") in the individual and was not inherited from a parent. The current estimated incidence of ALGS is approximately 1/30,000 –1/45,000.

Alagille syndrome can be associated with abnormalities of the liver, heart, eyes, skeleton, kidneys and other organ systems of the body. A main finding of Alagille syndrome is liver disease that often becomes apparent within the first three months of life. However, individuals with mild liver involvement may not be diagnosed until later in life. 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.

Approximately 90 percent of individuals with Alagille syndrome have a reduced number of bile ducts (bile duct paucity) within the liver. Bile ducts are small tube-like structures that carry bile from the liver to the small intestines. The formation of bile is one of the functions of the liver. Bile is a fluid that contains water, certain minerals that carry an electric charge (electrolytes), and other materials including bile salts, phospholipids, cholesterol, and an orange-yellow pigment (bilirubin) that is a byproduct of the natural breakdown of the hemoglobin of red blood cells. Bile flow accomplishes two important tasks within the body: it aids in digestion and absorption of dietary fats, vitamins, and other nutrients and helps eliminate excess cholesterol, bilirubin, waste, and toxins from the body. Therefore, a problem with bile flow often results in malabsorption of vital nutrients and the accumulation of toxic materials in the body.

Because of the reduced number of bile ducts, individuals with Alagille syndrome can develop jaundice and cholestasis usually during the first four months of life. Cholestasis refers to reduced or obstructed flow of bile from the liver. Cholestasis can cause yellowing of the skin (jaundice) or whites of the eyes (icterus), itching (pruritus) that may be intense, pale-colored stools, dark urine, fatty bumps (xanthomas) just under the surface of the skin, and an abnormally enlarged liver (hepatomegaly) and/or enlarged spleen (splenomegaly). Because the body cannot properly absorb fats and fat-soluble vitamins (vitamins A, D, E, and K), affected children may also experience growth deficiencies and failure to thrive. Malabsorption of vital nutrients can also lead to rickets, a condition marked by softened, weakened bones (vitamin D deficiency), vision problems (vitamin A deficiency), poor coordination and developmental delays (vitamin E deficiency) and blood clotting problems (vitamin K deficiency).

In approximately 15 percent of patients, progressive liver disease results in scarring of the liver (cirrhosis) and liver failure. There is no way to tell which children are at risk for serious, progressive liver disease in Alagille syndrome.

Many individuals with Alagille syndrome have heart (cardiac) abnormalities that can range from benign heart murmurs to serious structural defects. A heart murmur is an extra sound that is heard during a heartbeat. Heart murmurs in children with Alagille syndrome are usually caused by narrowing of the blood vessels of the lungs (pulmonary artery stenosis). The most common heart abnormality is peripheral pulmonary stenosis in which some of the blood vessels carrying blood to the lungs (pulmonary arteries) are narrowed (stenosis).

Some children with Alagille syndrome may have complex heart defects, the most common of which is tetralogy of Fallot. Tetralogy of Fallot is a rare form of cyanotic heart disease. Cyanosis is abnormal bluish discoloration of the skin and mucous membranes that occurs due to low levels of circulating oxygen in the blood. Tetralogy of Fallot consists of a combination of four different heart defects: ventricular septal defect, obstructed outflow of blood from the right ventricle to the lungs due to an abnormal narrowing of the opening between the pulmonary artery and the right ventricle of the heart (pulmonary stenosis), displaced aorta that causes blood to flow into the aorta from both the right and left ventricles, and abnormal enlargement of the right ventricle.

Additional heart defects that can occur in Alagille syndrome include ventricular septal defects, atrial septal defects, patent ductus arteriosus, and coarctation of the aorta. Some studies have shown that in rare cases there is an association with Wolff-Parkinson-White syndrome, a condition characterized by electrical disturbances in the heart. (For more information on these disorders, choose the specific disorder name as your search term in the Rare Disease Database.)

Some individuals with Alagille syndrome may have eye (ocular) abnormalities, especially posterior embryotoxon, a condition marked by thickening of the ring that normally lines the cornea in the eye. The cornea is the thin, transparent membrane that covers the eyeballs. In most cases, posterior embryotoxon is a benign finding that primarily helps to establish a clinical diagnosis and vision is usually unaffected, although mild decreases in the clarity of vision may occur. Less commonly, other eye abnormalities may occur such as Axenfeld anomaly, a condition in which strands of the iris are abnormally attached to the cornea, or progressive degeneration of the retina (pigmentary retinopathy). The retina is the thin layers of nerve cells that lines that inner surface of the back of the eyes and senses light and converts it to nerve signals, which are then relayed to the brain through the optic nerve.

Individuals with Alagille syndrome usually have distinctive facial features including deeply set and widely spaced (hypertelorism) eyes, a pointed chin, broad forehead, and low-set, malformed eyes. In older individuals and adults, the chin may appear larger and more prominent (prognathia). Skeletal abnormalities may occur in some individuals with Alagille syndrome including butterfly vertebrae, a condition in which certain bones of the spinal column are irregularly shaped. This condition is often noted on an x-ray, but usually does not cause any symptoms or problems (asymptomatic). Additional symptoms may occur in some individuals with Alagille syndrome including kidney (renal) abnormalities, pancreatic insufficiency, vascular anomalies, mild developmental delays and cognitive impairment. Kidney abnormalities may be more prevalent in individuals with Alagille syndrome caused by mutations in the NOTCH2 gene and include abnormally small kidneys, the presence of cysts on the kidneys and decreased or impaired kidney function. The pancreas is a small organ located behind the stomach that secretes enzymes that travel to the intestines and aid in digestion. The pancreas also secretes other hormones such as insulin, which helps to break down sugar. Pancreatic insufficiency is when the pancreas cannot produce or transport enough enzymes to the intestines to aid in the breakdown and absorption of food and nutrients.

Individuals with Alagille syndrome can also develop abnormalities of certain blood vessels (vascular anomalies) including those in the brain, liver, lungs, heart, and kidneys. Vascular anomalies in the brain can lead to bleeding inside the brain (intracranial bleeding) and stroke. Some individuals with Alagille syndrome have developed a condition known as Moyamoya syndrome. Moyamoya syndrome is a progressive disorder that is characterized by narrowing (stenosis) and/or closing (occlusion) inside the skull of the carotid artery, the major artery that delivers blood to the brain. Intracranial bleeding and other vascular anomalies are potentially life-threatening complications and account for a significant percentage of mortality and morbidity in Alagille syndrome.

Medical management is supportive, focusing on specific symptoms of disease. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, gastroenterologists, cardiologists, ophthalmologists, and other healthcare professionals may need to systematically and comprehensively plan an affect child's treatment. Individuals with Alagille syndrome should have a baseline echocardiogram (ultrasound of the heart) to screen for heart involvement, ultrasound of the abdomen to screen for liver and

kidney anomalies, and a screening eye (ophthalmology) exam, In addition, if not previously obtained for specific symptoms, a screening imaging study of the blood vessels of the head (MRI/MRA) is recommended for children who are old enough to sit through the study without need for anesthesia or sedation. Supplemental treatment with vitamins and nutrients is essential for individuals with malabsorption. Such treatment may include restoring vitamins A, D, E and K. Young children may be given formula with medium chain triglycerides because this form of fat is better absorbed by individuals with Alagille syndrome who have cholestasis. Some affected children may need to receive extra calories through a tube that runs from the nose to the stomach (nasogastric tube) or through a tube placed directly into the stomach through a small incision in the abdominal wall and stomach (gastrostomy tube).

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. 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.

Some affected infants and children with Alagille syndrome who do not respond to drug and dietary therapies may be treated by a surgical procedure known as partial biliary diversion. This surgical procedure is used to disrupt or divert recirculation of bile acids between the liver and the gastrointestinal tract. This therapy has demonstrated that, in some children, it can improve certain symptoms such as reducing itchiness or xanthoma formation.

In severe cases of Alagille syndrome (i.e., cases that have progressed to cirrhosis or liver failure or in which other therapies were unsuccessful), liver transplantation may be required.

Additional complications that can be associated with Alagille syndrome including heart, blood vessel and kidney abnormalities are treated in the standard manner. In some cases, this may include surgery.

The FDA approval of Bylvay (odevixibat) in ALGS is supported by data from the ASSERT trial, a double-blind, randomized, placebo-controlled trial designed to evaluate the safety and efficacy of 120 µg /kg/day Bylvay for 24 weeks in relieving pruritus in patients with ALGS. The trial enrolled 52 pediatric patients aged 6 months to 15 years of age with a genetically confirmed diagnosis of ALGS. Patients treated with BYLVAY demonstrated greater improvement in pruritus compared with placebo: Mean difference vs Placebo (95% CI) -0.9 (-1.4, -0.3) with p-value 0.002. More than 90% of patients were pruritus responders and the treatment arm also reached statistical significance in the secondary endpoint of reduction in serum bile acid concentration from baseline. Most common adverse drug reactions were diarrhea, abdominal pain, hematoma, and decreased weight.

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

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

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

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: References	Q1 2025
REVISION- Notable revisions: Required Medical Information FDA-Approved Uses References	Q1 2024
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Age Restrictions Quantity FDA-Approved Uses Background References	Q4 2023
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