Clinical Policy: Odevixibat (Bylvay)

Reference Number: CP.PHAR.528
Effective Date: 07.20.21
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Odevixibat (Bylvay™) is a non-systemic ileal bile acid transport inhibitor.

FDA Approved Indication(s)

Bylvay is indicated for the treatment of:

- Pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC)
- Cholestatic pruritus in patients 12 months of age and older with Alagille syndrome (ALGS)

Limitation(s) 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).

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Bylvay is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Progressive Familial Intrahepatic Cholestasis (must meet all)**:**

1. Diagnosis of genetically confirmed PFIC type 1 or 2 (formerly known as Byler disease or syndrome) with presence of both of the following (a and b):
   a. Pruritus requiring at least medium scratching (e.g., ≥ 2 on 0 to 4 scale);
   b. Serum bile acids (sBA) ≥ 100 µmol/L;
2. Prescribed by or in consultation with a hepatologist or gastroenterologist;
3. Age ≥ 3 months;
4. For PFIC type 2, member does not have pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein;
5. Member does not have portal hypertension or history of a hepatic decompensation event;
6. Failure of ursodeoxycholic acid, unless contraindicated or clinically significant adverse effects are experienced;[†]

   **Prior authorization may be required for ursodeoxycholic acid*
   [†]For Illinois HIM requests, the step therapy requirement above does not apply as of 1/1/2026 per IL HB 5395

7. Failure of an agent used for symptomatic relief of pruritus (e.g., antihistamine, rifampin, cholestyramine), unless clinically significant adverse effects are experienced or all are contraindicated;†
   †For Illinois HIM requests, the step therapy requirement above does not apply as of 1/1/2026 per IL HB 5395
8. Bylvay is not prescribed concurrently with other IBAT inhibitors (e.g., Livmarli®);
9. Documentation of member's current weight in kg;
10. Dose does not exceed one of the following (a, b, or c):
    a. 40 mcg/kg per day, not to exceed the recommended dose and quantity by body weight as outlined in Section V;
    b. 80 mcg/kg per day (up to a maximum of 6 mg per day), and documentation supports no improvement in pruritus after 3 months at a dose of 40 mcg/kg per day;
    c. 120 mcg/kg per day (up to a maximum of 6 mg per day), and documentation supports no improvement in pruritus after 3 months at a dose of 80 mcg/kg per day.

Approval duration: 6 months

B. Alagille Syndrome (must meet all)**:**
1. Diagnosis of ALGS-associated pruritus confirmed by one of the following (a or b):
   a. Genetic confirmation with presence of a mutation in *JAG1* or *NOTCH2*;
   b. Clinical confirmation of both of the following (i and ii):
      i. Bile duct paucity on liver biopsy;
      ii. Criteria meeting ≥ 3 of the 5 major criteria (*see Appendix G*);
2. Prescribed by or in consultation with hepatologist or gastroenterologist;
3. Age ≥ 12 months;
4. Age ≤ 17 years at therapy initiation;
5. Pruritus requiring at least medium scratching (e.g., ≥ 2 on 0-4 scale);
6. Evidence of cholestasis that is met by ≥ 1 of the following (a – e):
   a. Total sBA > 3 times upper limit of normal (ULN) for age;
   b. Conjugated bilirubin > 1 mg/dL;
   c. Fat-soluble vitamin deficiency otherwise unexplainable;
   d. Gamma-glutamyl transferase > 3 times ULN for age;
   e. Intractable pruritus explainable only by liver disease;
7. Member does not have portal hypertension or history of a hepatic decompensation event;
8. Failure of ursodeoxycholic acid, unless contraindicated or clinically significant adverse effects are experienced;†
   **Prior authorization may be required for ursodeoxycholic acid*
   †For Illinois HIM requests, the step therapy requirement above does not apply as of 1/1/2026 per IL HB 5395
9. Failure of an agent used for symptomatic relief of pruritus (e.g., antihistamine, rifampin, cholestyramine), unless clinically significant adverse effects are experienced or all are contraindicated;†
   †For Illinois HIM requests, the step therapy requirement above does not apply as of 1/1/2026 per IL HB 5395
10. Bylvay is not prescribed concurrently with other IBAT inhibitors (e.g., Livmarli®);

11. Documentation of member's current body weight in kilograms;
12. Dose does not exceed 120 mcg/kg per day, not to exceed the recommended dose and quantity by body weight as outlined in Section V.

Approval duration: 6 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Progressive Familial Intrahepatic Cholestasis (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters:
   a. Improvement in pruritus;
   b. Reduction of sBA from baseline;
3. Bylvay is not prescribed concurrently with other IBAT inhibitors (e.g., Livmarli®);
4. Documentation of member's current weight in kg;
5. If request is for a dose increase, new dose does not exceed one of the following (a, b, or c):
   a. 40 mcg/kg per day, not to exceed the recommended dose and quantity by body weight as outlined in Section V;
   b. 80 mcg/kg per day (up to a maximum of 6 mg per day), and documentation supports no improvement in pruritus after 3 months at a dose of 40 mcg/kg per day;

c. 120 mcg/kg per day (up to a maximum of 6 mg per day), and documentation supports no improvement in pruritus after 3 months at a dose of 80 mcg/kg per day.

Approval duration: 12 months

B. Alagille Syndrome (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by an improvement in pruritus;
3. Bylvay is not prescribed concurrently with other IBAT inhibitors (e.g., Livmarli®);
4. Documentation of member's current body weight in kilograms;
5. If request is for a dose increase, new dose does not exceed 120 mcg/kg per day, not to exceed the recommended dose and quantity by body weight as outlined in Section V.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ABCB11: ATP binding cassette subfamily B member 11
ALGS: Alagille syndrome
BSEP-3: bile salt export pump 3
FDA: Food and Drug Administration
IBAT: ileal bile acid transporter
ObsRO: observer-reported outcome
PFIC: progressive familial intrahepatic
sBA: serum bile acid
ULN: upper limit of normal

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ursodeoxycholic acid (Ursodiol®)*	15-30 mg/kg/day	30 mg/kg/day
Example of therapies for pruritus: antihistamine, rifampin, cholestyramine	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information
- Initial care for patients with PFIC targets symptoms and nutritional problems, including fat-soluble vitamin supplementation.
- Off-label conventional treatment for PFIC pruritus includes antihistamines, rifampin, and cholestyramine. In the pivotal PEDFIC 1 study, 85% of placebo and 57.1% of Bylvay patients were already receiving rifampicin.
- Ursodiol is usually considered first line therapy for all PFIC types and has been proven to improve liver function and pruritus. Use of Ursodiol is supported by expert opinion; additionally, in the pivotal PEDFIC 1 study, 90% of placebo and 76.2% of Bylvay patients were already receiving Ursodiol.
- Other PFIC options include surgical options such as nasobiliary drainage, partial external biliary diversion, and liver transplant.
- The PEDFIC 1 study only enrolled patients with PFIC type 1 or 2. PEDFIC 2 is an ongoing open-label extension of PEDFIC 1 and includes patients with other types of PFIC; however, results are not yet available.
- Bylvay will not work on PFIC type 2 with ABCB11 variants that encode for absence of BSEP-3 since Bylvay acts on the bile acid transporter. Therefore, in patients missing the BSEP-3 transporter, Bylvay may not inhibit the bile salt export pump.

Appendix E: Observer-Reported Outcome (ObsRO) Instrument for Pruritus
- 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 scale (0-4):
  - 0: no scratching

- 1: a little scratching
- 2: medium scratching
- 3: a lot of scratching
- 4: worst possible scratching

Appendix F: Genetic Confirmation of PFIC

- PFIC 1
  - Protein deficiency: FIC1
  - Mutated gene: ATP8B1
- PFIC 2
  - Protein deficiency: BSEP
  - Mutated gene: ABCB11

Appendix G: Classic Criteria, Based on Five Body Systems, for a Diagnosis of ALGS

Classic Criteria	Description
Liver/cholestasis	Usually presenting as jaundice with conjugated hyperbilirubinemia in the neonatal period, often with pale stools
Dysmorphic facies	Broad forehead, deep-set eyes, sometimes with upslanting palpebral fissures, prominent ears, straight nose with bulbous tip, and pointed chin giving the face a somewhat triangular appearance
Heart disease	Most frequently peripheral pulmonary artery stenosis, but also pulmonary atresia, atrial septal defect, ventricular septal defect, and Tetralogy of Fallot
Axial skeleton/vertebral anomalies	Characteristic 'butterfly' vertebrae may be seen on an antero-posterior radiograph, and occasionally hemivertebrae, fusion of adjacent vertebrae, and spina bifida occulta
Eye/posterior embryotoxon	Anterior chamber defects, most commonly posterior embryotoxon, which is prominence of Schwalbe's ring at the junction of the iris and cornea

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen*</th><th>Maximum Dose</th></tr>
<tr><td>ALGS</td><td>The recommended dose is 120 mcg/kg PO AM with a meal.

Recommended dosage/quantity for 120 mcg/kg/day:
<table>
<tr><th>Body weight (kg)</th><th>Total daily dose (mcg)</th></tr>
<tr><td>≤ 7.4</td><td>600 (1 oral pellet)</td></tr>
<tr><td>7.5 to 12.4</td><td>1,200 (2 oral pellets)</td></tr>
<tr><td>12.5 to 17.4</td><td>1,800 (3 oral pellets)</td></tr>
<tr><td>17.5 to 25.4</td><td>2,400 (2 capsules)</td></tr>
<tr><td>25.5 to 35.4</td><td>3,600 (3 capsules)</td></tr>
<tr><td>35.5 to 45.4</td><td>4,800 (4 capsules)</td></tr>
<tr><td>45.5 to 55.4</td><td>6,000 (5 capsules)</td></tr>
<tr><td>≥ 55.5</td><td>7,200 (6 capsules)</td></tr>
</table></td><td>120 mcg/kg/day</td></tr>
</table>

Indication	Dosing Regimen*	Maximum Dose
PFIC	The recommended dose is 40 mcg/kg PO AM 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 PO QD not to exceed a total daily dose of 6 mg. **Recommended dosage/quantity for 40 mcg/kg/day**:	6 mg/day

Body weight (kg)	Total daily dose (mcg)
≤ 7.4	200 (1 oral pellet)
7.5 to 12.4	400 (2 oral pellets)
12.5 to 17.4	600 (1 oral pellets)
17.5 to 25.4	800 (2 capsules)
25.5 to 35.4	1,200 (1 capsule)
35.5 to 45.4	1,600 (2 capsules)
45.5 to 55.4	2,000 (3 capsules)
≥ 55.5	2,400 (2 capsules)

**Bylvay oral pellets are intended for use by patients weighing < 19.5 kg, while the capsules are intended for use by patients weighing ≥ 19.5 kg.*

VI. Product Availability

- Oral pellets: 200 mcg, 600 mcg
- Capsules: 400 mcg, 1,200 mcg

VII. References

1. Bylvay Prescribing Information. Boston, MA: Albireo Pharma, Inc.; February 2024. Available at: https://bylvay.com/. Accessed January 16, 2025.

Progressive Familial Intrahepatic Cholestasis

2. Thompson RJ, Arnell H, Artan R, et al. Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol. 2022;7(9):830-842.
3. Long term safety & efficacy study evaluating the effect of A4250 in children with PFIC (PEDFIC 2). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03659916. Accessed February 9, 2025.
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5. Davit-Spraul A, Gonzales E, Baussan C, and Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet Journal of Rare Diseases. 2009; 4:1. doi:10.1186/1750-1172-4-1.
6. Gunaydin M and Cil A. Progressive familial intrahepatic cholestasis: Diagnosis, management, and treatment. Hepatic Medicine: Evidence and Research. 2018; 10: 95-104.
7. Baker A, Kerkar N, Todorova L, Kamath BM, and Houwen RHJ. Systematic review of progressive familial intrahepatic cholestasis. Clinics and Research in Hepatology and Gastroenterology. 2019; 43: 20-36.

8. Hirschfield GM, Heathcote EJ, and Gerswhin ME. Pathogenesis of cholestatic liver disease and therapeutic approaches. Reviews in Basic and Clinical Gastroenterology and Hepatology. 2010; 139(5): 1481-1496.
9. Progressive Familial Intrahepatic Cholestasis Advocacy and Resource Network. Diagnosis and treatment. Available at https://www.pfic.org/diagnosis-and-treatment-of-pfic/. Accessed February 9, 2025.

Alagille Syndrome

10. Ayoub MD, Kamath BM. Alagille syndrome: Current understanding of pathogenesis, and challenges in diagnosis and management. Clin Liver Dis. 2022 Aug;26(3):355-370. doi: 10.1016/j.cld.2022.03.002. Epub 2022 Jun 25. PMID: 35868679.
11. Kohut TJ, Gilbert MA, Loomes KM. Alagille syndrome: A focused review on clinical features, genetics, and treatment. Semin Liver Dis. 2021 Nov;41(4):525-537.
12. Ovchinsky N, Aumar M, Baker A, et al. Efficacy and safety of odevixibat in patients with Alagille syndrome (ASSERT): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2024;9(7):632-645.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	04.13.21	05.21
Drug is now FDA approved - criteria updated per FDA labeling: modified age restriction; removed minimum body weight restriction; updated dosing requirements to include allowable escalations; references reviewed and updated.	07.21.21	08.21
RT1: added requirement for documentation of current body weight; added appendices D-F; references reviewed and updated.	08.31.21	11.21
2Q 2022 annual review: modified rifampicin references to rifampin as there are no rifampicin products currently marketed; references reviewed and updated.	02.04.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.04.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	02.05.23	05.23
RT4: added newly FDA-approved indication for ALGS.	06.27.23	
2Q 2024 annual review: added exclusions for portal hypertension and history of a hepatic decompensation event for both PFIC and ALGS per competitor analysis; references reviewed and updated.	01.10.24	05.24
2Q 2025 annual review: for initial and continued therapy, added exclusion for concurrent use with other IBAT inhibitors; for exclusion of pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein, clarified this is specific to PFIC type 2; references reviewed and updated.	03.06.25	05.25
Added step therapy bypass for IL HIM per IL HB 5395.	09.08.25	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.