Clinical Policy: Odevixibat (Bylvay)

Reference Number: PA.CP.PHAR.528
Effective Date: 10/2021
Last Review Date: 07/2023

Revision Log

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

FDA Approved Indication(s)
Bylvay is indicated for the treatment:

- 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 PFIC type 2 patients with 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 PA Health & Wellness® 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, 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 ≥ 100 µmol/L;
2. Prescribed by or in consultation with a hepatologist or gastroenterologist;
3. Age ≥ 3 months;
4. Member does not have pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein;
5. Failure of ursodeoxycholic acid, unless contraindicated or clinically significant adverse effects are experienced;
6. 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;
7. Documentation of member's current weight in kg;
8. 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.
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 serum bile acid > 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. Failure of ursodeoxycholic acid, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for ursodeoxycholic acid*
8. 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;
9. Documentation of member's current body weight in kilograms;
10. 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

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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 serum bile acids from baseline;

3. Documentation of member's current weight in kg;
4. 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. Documentation of member's current body weight in kilograms;
4. 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. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 – PA.CP.PMN.53

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
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: anthistamine, 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 19.4</td><td>2,400 (4 oral pellets)</td></tr>
<tr><td>19.5 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>
<tr><td>PFIC</td><td>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:
<table>
<tr><th>Body weight (kg)</th><th>Total daily dose (mcg)</th></tr>
<tr><td>≤ 7.4</td><td>200 (1 oral pellet)</td></tr>
<tr><td>7.5 to 12.4</td><td>400 (2 oral pellets)</td></tr>
<tr><td>12.5 to 17.4</td><td>600 (3 oral pellets)</td></tr>
<tr><td>17.5 to 19.4</td><td>2,400 (4 oral pellets)</td></tr>
<tr><td>19.5 to 25.4</td><td>2,400 (2 capsules)</td></tr>
<tr><td>25.5 to 35.4</td><td>1,200 (1 capsule)</td></tr>
<tr><td>35.5 to 45.4</td><td>1,600 (2 capsules)</td></tr>
<tr><td>45.5 to 55.4</td><td>2,000 (3 capsules)</td></tr>
<tr><td>≥ 55.5</td><td>2,400 (2 capsules)</td></tr>
</table></td><td>6 mg/day</td></tr>
</table>

**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.; June 2023. Available at: https://bylvay.com/. Accessed June 22, 2023.
2. This study will investigate the efficacy and safety of A4250 in children with PFIC 1 or 2 (PEDFIC 1). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03566238. Accessed August 5, 2021.

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, 2021.
4. Albireo phase 3 trial meets both primary endpoints for odevixibat in PFIC. Press release available at: https://ir.albireopharma.com/news-releases/news-release-details/albireo-phase-3-trial-meets-both-primary-endpoints-odevixibat. Executive summary available at: https://ir.albireopharma.com/static-files/d3df0f8f-336f-45eb-b6df-2d08e5e99596. Published September 8, 2020. Accessed February 9, 2021.
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.
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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. Efficacy and safety of odevixibat in patients with Alagille syndrome (ASSERT). ClinicalTrials.gov Identifier: NCT02160782. Available at: https://clinicaltrials.gov/ct2/show/NCT04674761. Assessed March 16, 2023.
13. Albireo reports positive topline data from phase 3 trial of Bylvay (odevixibat) in Alagille syndrome. October 11, 2022. Available at: https://ir.albireopharma.com/news-releases/news-release-details/albireo-reports-positive-topline-data-phase-3-trial-bylvayr. Accessed March 16, 2023.
14. Efficacy and safety of odevixibat in patients with Alagille syndrome: top-line results from assert, a phase 3, double-blind, randomized, placebo-controlled study. 2022 American Association for Study of Liver Diseases congress. Available at: https://www.aasld.org/the-liver-meeting/efficacy-and-safety-odevixibat-patients-alagille-syndrome-top-line-results-assert. Accessed June 22, 2023.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	10/2021	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2022 annual review: modified rifampicin references to rifampin as there are no rifampicin products currently marketed; references reviewed and updated.	04/2022	
2Q 2023 annual review: no significant changes; references reviewed and updated.	04/2023	
RT4: added newly FDA-approved indication for ALGS.	07/2023	