Drug Monograph

Drug Name: **Bylvay™ (odevixibat) capsules and pellets**
Drug Class: **Gastrointestinal: Bile Salt Agents**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Bylvay is available in 400 mcg and 1200 mcg capsules and 200 mcg and 600 mcg pellets.
Manufacturer:	Distributed by: Albireo Pharma, Boston, MA 02109.
Summary of Findings:	The safety and efficacy of Bylvay was shown in the PEDFIC 1, a randomized, double-blind, placebo-controlled, Phase 3, 24-week trial in which patients were randomized to receive Bylvay 40 mcg/kg daily, 120 mcg/kg daily, or placebo. Participants (N=62) were required to have a confirmed molecular diagnosis of PFIC Type 1 or 2 and the presence of moderate pruritus at baseline. The primary outcome measure was change in positive pruritus assessment compared to placebo at the subject level over the 24 week treatment period. Patients treated with Bylvay demonstrated greater improvement in pruritis compared with placebo. About 85% of the patients experienced adverse effects, the most common being diarrhea, increased ALT/AST, vomiting, abdominal pain, and fat-soluble vitamin deficiency.

Status Recommendation:	☐ Clinical Edit ☐ Open Access	☐ PA Required ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☐ No PA Required	☒ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Progressive familial intrahepatic cholestasis (PFIC) is a group of rare autosomal recessive liver disorders characterized by mutations in genes encoding proteins involved in the hepatocellular transport system. The genetic mutations lead to a disruption in bile formation. Under normal conditions, bile acids are produced in the liver utilizing cholesterol and are stored in the gallbladder. Bile acids are released into the small intestine in response to food and are essential for digestion and the absorption of dietary fats and fat-soluble vitamins (vitamins A, D, E, and K). Following digestion, bile acids are reclaimed in the distal part of the small intestine, the terminal ileum, by the ileal bile acid transporter (IBAT). IBAT initiates the transport of bile acids back through the portal vein and into the liver via enterohepatic circulation. Defects along this pathway can result in the build-up of toxic bile acids, leading to hepatocyte damage, inflammation, and liver injury. Cholestasis is the hallmark sign of PFIC, and is associated with jaundice, malabsorption, and intense pruritus. Patients can also present with splenomegaly, hepatomegaly, and impaired growth. The pruritus associated with PFIC is often described as the most bothersome symptom and may lead to bleeding, excoriations, scars, and discomfort that impacts activities of daily living and sleep. The exact mechanism by which pruritus occurs is unknown but it is proposed that the itching is induced via the stimulation of nonmyelinated subepidermal free nerve ends resulting from increased serum bile acids. There are three main subtypes of PFIC: Types 1, 2, and 3. The most severe forms, Types 1 and 2, are caused by a depletion of bile acid secretion. Type 3, the rarest form, is the result of impaired bile phospholipid secretion. Although the affected gene differs between subtypes, all are caused by defects in the genes that encode proteins associated with the hepatocellular transport system. PFIC typically develops in infancy with a median age of symptom onset of 2 months with 78% of patients developing jaundice but it can also develop into young adulthood. There are an estimated 600 cases of PFIC in the United States and 15,000 worldwide. Incidence is estimated at 1 in 50,000 to 1 in 100,000 births. Disease progression can occur rapidly with resultant fibrosis and end-stage liver disease occurring before adulthood. Additional complications include portal hypertension, cirrhosis, and hepatocellular carcinoma. If left untreated, PFIC is fatal.

Dosage Form [3]

Bylvay is available in 400 mcg and 1200 mcg capsules and 200 mcg and 600 mcg pellets.

Manufacturer [3]

Distributed by: Albireo Pharma, Boston, MA 02109.

Indication(s) [3]

Bylvay is indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Bylvay is a non-systemic reversible inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum.

Pharmacokinetics:

Absorption	C_{max}: 1 to 5 hours
Metabolism	Via mono-hydroxylation
Excretion	Fecal (82.9%)
Half-life	$t_{½}$: 2.36 hours

Clinical Trials Experience

STUDY DESIGN (PEDFIC 1; NCT03566238)	Randomized, double-blind, placebo-controlled, Phase 3, 24-week efficacy and safety study (N=62)
INCLUSION CRITERIA	• Clinical diagnosis of PFIC Type 1 or 2 and body weight above 5 kg • Genetic confirmation of PFIC 1 or PFIC 2 • History of significant pruritis (average scratching score ≥ 2 [medium scratching])
EXCLUSION CRITERIA	• Pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein • INR > 1.4 • ALT or total bilirubin > 10 times upper limit of normal • Past medical history or ongoing presence of other types of liver disease (e.g., biliary atresia, benign recurrent intrahepatic cholestasis) • Biliary diversion surgery within 6 months prior to start of screening period • Liver transplant or planned liver transplant within 6 months of randomization • Decompensated liver disease
TREATMENT REGIMEN	Patients were randomized to placebo (n=20), Bylvay 40 mcg/kg (n=23), or Bylvay 120 mcg/kg (n=19) once daily.
RESULTS	• Primary Outcome Measure: proportion of positive pruritus assessments compared to placebo at the subject level over the 24 week treatment period based on the Albireo observer-reported outcome (ObsRO) instrument. • A positive pruritus assessment was defined as a scratching score of ≤ 1 or at least a one-point drop from baseline on the Albireo ObsRO instrument. Scratching measured twice daily on a scale of 0 (no scratching) to 4 (worst possible scratching).

	Bylvay 40 mcg/kg/day (n=23)	**Bylvay 120 mcg/kg/day (n=19)**	**Placebo (n=20)**
Mean[a] Percentage of Assessments Over the Treatment Period Scored as 0 (no Scratching) or 1 (a little scratching) (%)*			
Mean (SE)	35.4 (8.1)	30.1 (9.0)	13.2 (8.7)

	Mean Difference vs. Placebo (95% CI)	22.2 (4.7, 39.6)	16.9 (-2.0, 35.7)	
	** 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).* *[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.*			
SAFETY	Discussed in the Adverse Effects section below.			

Contraindications [3,4]

- None known

Warnings and Precautions [3,4]

- Liver Test Abnormalities: Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be required if abnormalities occur. For persistent or recurrent liver test abnormalities, consider treatment discontinuation.
- Diarrhea: Treat dehydration. Treatment interruption or discontinuation may be required for persistent diarrhea.
- Fat-Soluble Vitamin (FSV) Deficiency: Obtain baseline levels and monitor during treatment. Supplement if deficiency is observed. If FSV deficiency persists or worsens despite FSV supplementation, discontinue treatment.

Adverse Effects [3,4]

Most common, ≥2%	Bylvay 40 mcg/kg/day N=23 n (%)	Bylvay 120 mcg/kg/day N=19 n (%)	Total Bylvay N=42 n (%)	Placebo N=20 n (%)
Diarrhea	9 (39.1)	4 (21.1)	13 (31)	2 (10)
Transaminases increased (ALT, AST)	3 (13)	4 (21.1)	7 (16.7)	1 (5)
Vomiting	4 (17.4)	3 (15.8)	7 (16.7)	0
Abdominal pain	3 (13)	3 (15.8)	6 (14.3)	0
Blood bilirubin increased	3 (13)	2 (10.5)	5 (11.9)	2 (10)
FSV deficiency (A, D, E)	0	3 (15.8)	3 (7.1)	1 (5)
Splenomegaly	0	2 (10.5)	2 (4.8)	0
Cholelithiasis	0	1 (5.3)	1 (2.4)	0
Dehydration	0	1 (5.3)	1 (2.4)	0
Fracture	1 (4.3)	0	1 (2.4)	0

Drug Interactions [3,4]

- Bile Acid Binding Resins: Administer bile acid binding resins (e.g., cholestyramine, colesevelam, or colestipol) at least 4 hours before or 4 hours after administration of Bylvay. Bile acid binding resins may bind Bylvay in the gut, which may reduce Bylvay efficacy.

Dosage and Administration [3,4]

- The recommended dosage of Bylvay is 40 mcg/kg once daily in the morning with a meal. Bylvay must not be mixed with liquids; capsules containing oral pellets may be opened and contents mixed into soft food.
- If no improvement in pruritus after 3 months, the dosage may be increased in 40 mcg/kg increments up to 120 mcg/kg once daily to not exceed a total daily dose of 6 mg.

Weight-Based Recommended Dosage for 40 mcg/kg/day

Body Weight (kg)	Total Daily Dose (mcg)
7.4 and below	200
7.5 to 12.4	400
12.5 to 17.4	600
17.5 to 25.4	800
25.5 to 35.4	1200
35.5 to 45.4	1600
45.5 to 55.4	2000
55.5 and above	2400

- Bylvay pellets are intended for use by patients weighing less than 19.5 kilograms.
- Bylvay capsules are intended for use by patients weighing 19.5 kilograms and above.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Odevixibat	Bylvay™	Albireo Pharma	40 mcg/kg orally once daily	~$26,400 (for 18 kg patient)

** Wholesale Acquisition Cost

Conclusion

Bylvay is a non-systemic reversible inhibitor of the IBAT. It decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum. It is indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis. The safety and efficacy of Bylvay was shown in the PEDFIC 1, a Phase 3, 24-week trial where patients were randomized to receive Bylvay 40 mcg/kg daily, 120 mcg/kg daily, or placebo. Both primary endpoints, change in pruritus assessment (p=0.004) and serum bile acid response (p=0.003), were met. About 85% of the patients experienced adverse effects, the most common being diarrhea, increased ALT/AST, vomiting, abdominal pain, and fat-soluble vitamin deficiency.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) PFIC: Research Library. Progressive Familial Intrahepatic Cholestasis Advocacy & Resource Network, Inc. https://www.pfic.org/research-library/. Accessed September 30, 2021.
2) IPD Analytics: New Drug Review: Bylvay (odevixibat). Accessed September 30, 2021.
3) Blyvay™ (odevixibat) [package insert]. Boston, MA: Albiero Pharma, Inc.; July 2021.

Prepared by: April Ash, PharmD

Date: September 30, 2021