PDL DRUG REVIEW

Proprietary Name: Bylvay®
Common Name: odevixibat
PDL Category: GI- Misc

Summary

Pharmacology/Usage: Odevixibat, the active ingredient of Bylvay®, is a reversible inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum. Although the complete mechanism by which odevixibat improves pruritus in progressive familial intrahepatic cholestasis (PFIC) patients is not known, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids.

Indication: For the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis . 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).

There is no pregnancy category for this medication; however, the risk summary indicates that there are no human data on use in pregnant persons to establish a drug-associated risk of major birth defects, miscarriage, or adverse developmental outcomes. Based on findings from animal studies, Bylvay® may cause cardiac malformations when a fetus is exposed during pregnancy. The safety and efficacy of use have not been established in pediatric patients less than 3 months of age.

Dosage Form: Available as:

- Oral Pellets: 200mcg and 600mcg
- Capsules: 400mcg and 1200mcg

Recommended Dosage: Take 40mcg/kg once daily in the morning with a meal. If there is no improvement in pruritus after 3 months, the dosage may be increased in 40mcg/kg increments up to 120mcg/kg once daily not to exceed a total daily dose of 6mg.

The table below includes the recommended weight-based total daily dosage needed for the recommended dosage at 40mcg/kg daily. Note that

- Bylvay® oral pellets are intended for use by patients weighing less than 19.5kg.
- Bylvay® capsules are intended for use by patients weighing 19.5kg or above.

Body weight (kg)	Total daily dose (mcg)
7.4 and below	200
7.5 to 12.4	400
12.5 to 17.4	600

Body weight (kg)	Total daily dose (mcg)
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

For the oral pellets, mix the contents of the shell containing oral pellets into soft food. Do not mix Bylvay® in liquids. Do not swallow the shell containing oral pellets whole. Patients who are exclusively on liquid food should not use Bylvay®. To administer oral pellets, place a small amount of soft food (up to 30ml or 2 tablespoons) of apple sauce, oatmeal, banana or carrot puree, or chocolate or rice pudding) in a bowl. Keep food at or below room temperature. Open the shell containing the oral pellets and empty the contents into the bowl of soft food. Gently tap the oral pellet shell to ensure that all contents have been dispersed. If the dose requires more than one shell of oral pellets, repeat the steps above. Gently mix until well dispersed and administer the entire dose immediately, followed by water. Do not store mixture for future use.

For the capsules, swallow the capsules whole with a glass of water. Alternatively, for patients unable to swallow the capsules whole, Bylvay® capsules may be opened, and sprinkled and mixed with a small amount of soft food. Follow directions above for oral pellets to prepare and administer such a mixture.

Establish the baseline pattern of variability of liver tests prior to starting Bylvay®, so that potential signs of liver injury can be identified. Monitor liver tests (e.g. ALT, AST, total bilirubin, direct bilirubin) and INR during treatment with Bylvay®. Interrupt Bylvay® if new onset liver test abnormalities occur or symptoms consistent with clinical hepatitis are observed. Once the liver test abnormalities either return to baseline values or stabilize at a new baseline value, consider restarting Bylvay® at the lowest dose of 40mcg/kg, and increase as tolerated if appropriate. Consider discontinuing Bylvay® permanently if liver test abnormalities recur. Discontinue Bylvay® permanently if a patient experiences a hepatic decompensation event (e.g. variceal hemorrhage, ascites, hepatic encephalopathy).

Patients with PFIC may have impaired hepatic function at baseline. The efficacy and safety in PFIC patients with clinically significant portal hypertension and in patients with decompensated cirrhosis have not been established.

Drug Interactions: 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 odevixibat in the gut, which may reduce Bylvay® efficacy.

Box Warning: There is no box warning associated with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Bylvay®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than the placebo.* The most frequently reported adverse events included diarrhea (21%), transaminases increased (ALT, AST; 11.7%), vomiting (16.7%), abdominal pain (14.3%), blood bilirubin increased (1.9%), fat-soluble vitamin deficiency (A, D, E; 2.1%), splenomegaly (4.8%), cholelithiasis (2.4%), dehydration (2.4%), and fracture (2.4%).

Patients enrolled in the phase 3 clinical trial had abnormal liver tests at baseline. Treatment-emergent elevations of liver tests or worsening of liver tests relative to baseline values were observed during the clinical trial. Most abnormalities included elevation in AST, ALT, total bilirubin, or direct bilirubin. Treatment interruption days ranged from 3 days to 124 days, but none in this trial permanently discontinued treatment due to liver test abnormalities. Thus, obtain baseline liver tests and monitor during treatment. Dose reduction or interruption of treatment may be required if abnormalities occur. Bylvay® was not evaluated in PFIC patients with cirrhosis. Closely monitor for liver

test abnormalities; permanently discontinue Bylvay® if a patient progresses to portal hypertension or experiences a hepatic decompensation event.

Diarrhea was reported in the phase 3 clinical trial. Treatment interruption due to diarrhea occurred in 2 patients with 3 events during treatment with Bylvay® 120mcg/kg/day. Treatment interruption due to diarrhea ranged between 3 to 7 days. One patient treated with Bylvay® 120mcg/kg/day withdrew from the trial due to persistent diarrhea. If diarrhea occurs, monitor for dehydration, and treat promptly. Interrupt Bylvay® dosing if a patient experiences persistent diarrhea. Restart Bylvay® at 40mcg/kg/day when diarrhea resolves, and increase the dose as tolerated if appropriate. If diarrhea persists and no alternate etiology is identified, stop Bylvay® treatment.

Fat-soluble vitamins (FSV) include vitamin A, D, E, and K (measured using INR levels). PFIC patients can have FSV deficiency at baseline. Bylvay® may affect absorption of fat-soluble vitamins. Obtain serum FSV levels at baseline and monitor during treatment, along with any clinical manifestations. If FSV deficiency is diagnosed, supplement with FSV. Discontinue Bylvay® if FSV deficiency persists or worsens despite adequate FSV supplementation.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Albireo Pharma, Inc

Analysis: The safety and efficacy of Bylvay® were assessed in a randomized, double-blind, placebo-controlled trial of 24 week duration that included pediatric patients (Trial 1, N=62) aged 6 months to 17 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2 and the 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, or who had received a liver transplant were excluded.

The median age of included patients was 3.2 years (range 0.5 to 15.9 years), while 50% were male, 84% were white, 27% had PFIC type 1, and 73% had PFIC type 2. The mean scratching score in the 2 weeks prior to baseline was 2.9, baseline mean eGFR was 164ml/min/1.73m^2, baseline median ALT was 65U/L, baseline median AST was 83.5U/L, and baseline median total bilirubin was 2.2mg/dl. In this trial, a total of 13 patients discontinued from the trial prematurely due to no improvement in pruritus (N=11) or due to adverse reactions (N=2); 25% (N=5/20) of patients discontinued treatment in the placebo arm and 19% (N=8/42) discontinued in the Bylvay® arm. A total of 11 of the 13 patients rolled over to Trial 2 to receive Bylvay® 120mcg/kg/day.

Given the patient's young age, a single-item observer-reported outcome (ObsRO) was used to measure patient's scratching as observed by their caregiver twice daily. 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 ≥2 (medium scratching) in the 2 weeks prior to baseline. The table below, adapted from the prescribing information, presents the results of the comparison between treatment groups on the mean of patient's percentage of ObsRO assessments over the 24-week treatment period that were scored as 0 (no scratching) or 1 (a little scratching). Results suggested that patients treated with Bylvay® demonstrated greater improvement in pruritus compared with placebo.

Mean, % of assessments over the treatment period scored as 0 (no scratching) or 1 (a little scratching), %	Placebo (N=20)	Bylvay®	
		40mcg/kg/day (N=23)	120mcg/kg/day (N=19)
Mean	13.2%	35.4%	30.1%
Mean difference vs placebo		22.2%	16.9%
NNT *calculated by CHC*		5	6

Place in Therapy: Bylvay® is indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC). 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). Obtain baseline liver tests and monitor during treatment with Bylvay®. In addition, obtain serum fat-soluble vitamin (FSV) levels at baseline and monitor during treatment, along with any clinical manifestations. If FSV deficiency is diagnosed, supplement with FSV. In a 24-week, randomized, double-blind, placebo-controlled trial that included 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 (N=62), patients treated with Bylvay® demonstrated greater improvement in pruritus compared with placebo.

It is recommended that Bylvay® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**

References

[1] Bylvay [package insert]. Boston, MA: Albireo Pharma, Inc; 2021.

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