BYLVAY- odevixibat capsule, coated pellets
Albireo Pharma, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BYLVAY safely and effectively. See full prescribing information for BYLVAY.

BYLVAY (odevixibat) capsules, for oral use
BYLVAY (odevixibat) oral pellets
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

BYLVAY is an ileal bile acid transporter (IBAT) inhibitor indicated for the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC). (1)
Limitation 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).

DOSAGE AND ADMINISTRATION

- The recommended dosage is 40 mcg/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 40 mcg/kg increments up to 120 mcg/kg once daily not to exceed a total daily dose of 6 mg.

Administration:
- Administer BYLVAY in the morning with a meal.
- Do not crush or chew capsules.
- See prescribing information for administration instructions. (2.2)

DOSAGE FORMS AND STRENGTHS

Oral Pellets: 200 mcg, 600 mcg (3)
Capsules: 400 mcg, 1200 mcg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- 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. (5.1)
- Diarrhea: Treat dehydration. Treatment interruption or discontinuation may be required for persistent diarrhea. (5.2)
- 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. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (>2%) are liver test abnormalities, diarrhea, abdominal pain, vomiting, and fat-soluble vitamin deficiency. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Albireo Pharma, Inc. at +1-855-252-4736, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause cardiac malformations (8.1)
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitations 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).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- The recommended dosage of BYLVAY is 40 mcg/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 40 mcg/kg increments up to 120 mcg/kg once daily not to exceed a total daily dose of 6 mg.

Table 1 below shows the recommended weight-based total daily dosage needed for the recommended dosage at 40 mcg/kg once daily.

- BYLVAY oral 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 or above.

Table 1. 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

2.2 Preparation and Administration Instructions

- For patients taking bile acid binding resins, take BYLVAY at least 4 hours before or 4 hours after taking a bile acid binding resin *[see Drug Interactions (7.1)].*
- Do not crush or chew capsules.

Oral Pellets:

- Mix the contents of the shell containing oral pellet(s) 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.

  Administration Instructions:

  1. Take BYLVAY in the morning with a meal.
  2. Place a small amount of soft food (up to 30 mL [2 tablespoons] of apple sauce, oatmeal, banana or carrot puree, chocolate or rice pudding) in a bowl. Keep food at or below room temperature.
  3. Open the shell containing oral pellet(s) and empty the contents into the bowl of soft food. Gently tap the oral pellet shell to ensure that all contents have been dispersed.
  4. If the dose requires more than one shell of oral pellets, repeat step 2 and step 3.

5. Gently mix until well dispersed and administer the entire dose immediately.
6. Follow the dose with water.
7. Do not store mixture for future use.

Capsules:

Administration Instructions:

1. Take in the morning with a meal.
2. Swallow the capsule whole with a glass of water.
3. 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.

2.3 Dose Modification for Management of Adverse Events

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 [alanine aminotransferase], AST [aspartate aminotransferase], TB [total bilirubin], DB [direct bilirubin] and International Normalized Ratio [INR]) during treatment with BYLVAY. Interrupt BYLVAY if new onset liver test abnormalities occur or symptoms consistent with clinical hepatitis are observed [*see Warnings and Precautions (5.1)*].

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 40 mcg/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).

3 DOSAGE FORMS AND STRENGTHS

Oral Pellets:

- 200 mcg: capsule with ivory opaque cap and white opaque body; imprinted "A200" (black ink).
- 600 mcg: capsule with ivory opaque cap and body; imprinted "A600" (black ink).

Capsules:

- 400 mcg: capsule with medium orange opaque cap and white opaque body; imprinted "A400" (black ink).
- 1200 mcg: capsule with medium orange opaque cap and body; imprinted "A1200" (black ink).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Liver Test Abnormalities

Patients enrolled in the trial had abnormal liver tests at baseline. In Trial 1, 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, or total and direct bilirubin (see Table 2). Treatment interruption days ranged from 3 days to 124 days; none of the patients in Trial 1 permanently discontinued treatment due to liver test abnormalities *[see Adverse Reactions (6.1)].*

Table 2. Treatment-Emergent Elevation in Liver Tests in Trial 1

Number of Patients with:	**Placebo (N=20) n (%)**	**BYLVAY 40 mcg/kg (N=23) n (%)**	**BYLVAY 120 mcg/kg (N=19) n (%)**	**Total BYLVAY (N=42) n (%)**
ALT increase over baseline ≥150 U/L	0	2 (8.7)	2 (10.5)	4 (9.5)
AST increase over baseline by ≥150 U/L	0	1 (4.3)	3 (15.8)	4 (9.5)
TB increase over baseline by ≥2 mg/dL	1 (5.0)	4 (17.4)	1 (5.3)	5 (11.9)
DB increase over baseline by ≥1 mg/dL	2 (10.0)	5 (21.7)	2 (10.5)	7 (16.7)

ALT= alanine aminotransferase; AST= aspartate aminotransferase; DB= direct bilirubin; TB= total bilirubin; ULN= Upper Limit of Normal

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 *[see Dosage and Administration (2.3)].*

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.

5.2 Diarrhea

In Trial 1, diarrhea was reported in 2 (10%) placebo-treated patients, 9 (39%) BYLVAY-treated 40 mcg/kg/day patients and 4 (21%) BYLVAY-treated 120 mcg/kg/day patients. Treatment interruption due to diarrhea occurred in 2 patients with 3 events during treatment with BYLVAY 120 mcg/kg/day. Treatment interruption due to diarrhea ranged between 3 to 7 days *[see Adverse Reactions (6.1)]*. One patient treated with BYLVAY 120 mcg/kg/day withdrew from Trial 1 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 40 mcg/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.

5.3 Fat-Soluble Vitamin (FSV) Deficiency

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. In Trial 1, new onset or worsening of existing FSV deficiency was reported in 1 (5%) placebo-treated patient, and 3 (16%) BYLVAY-treated 120 mcg/kg/day patients; none of the BYLVAY-treated 40 mcg/kg/day patients had new onset or worsening of existing FSV deficiency *[see Adverse Reactions (6.1)].*

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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Liver enzyme abnormalities [*see Warnings and Precautions (5.1)*]
- Diarrhea *[see Warnings and Precautions (5.2)]*
- Fat-Soluble Vitamin Deficiency *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Trial 1 is a randomized, double-blind, placebo-controlled, 24-week study of two dose levels of BYLVAY (40 mcg/kg and 120 mcg/kg) administered once daily. Sixty-two patients were randomized (1:1:1) to receive one of the following:

- BYLVAY 40 mcg/kg/day (n=23),
- BYLVAY 120 mcg/kg/day (n=19), or
- Placebo (n=20).

Table 3 summarizes the frequency of clinical adverse events (AEs), regardless of causality, reported in ≥2% and at a rate greater than placebo in patients treated with BYLVAY in Trial 1. Overall, about 85% of patients experienced AEs. The most common adverse reactions observed in Trial 1 included diarrhea, liver test abnormalities, vomiting, abdominal pain, and fat-soluble vitamin deficiency.

Table 3. Clinical Adverse Reactions in Trial 1

Preferred Term	**Placebo N=20 n (%)**	**BYLVAY 40 mcg/kg/day N=23 n (%)**	**BYLVAY 120 mcg/kg/day N=19 n (%)**	**Total BYLVAY N=42 n (%)**
Any AE	17 (85.0)	19 (82.6)	16 (84.2)	35 (83.3)
Diarrhea	2 (10.0)	9 (39.1)	4 (21.1)	13 (31.0)
Transaminases increased (ALT, AST)	1 (5.0)	3 (13.0)	4 (21.1)	7 (16.7)
Vomiting	0	4 (17.4)	3 (15.8)	7 (16.7)
Abdominal pain	0	3 (13.0)	3 (15.8)	6 (14.3)

Blood bilirubin increased	2 (10.0)	3 (13.0)	2 (10.5)	5 (11.9)
Fat-soluble vitamin deficiency (A, D, E)	1 (5.0)	0	3 (15.8)	3 (7.1)
Splenomegaly	0	0	2 (10.5)	2 (4.8)
Cholelithiasis	0	0	1 (5.3)	1 (2.4)
Dehydration	0	0	1 (5.3)	1 (2.4)
Fracture	0	1 (4.3)	0	1 (2.4)

Trial 2 is a 72-week, open-label, single-arm trial in PFIC type 1, 2, and 3 patients. Age of the enrolled patients ranged from 4 months to 25 years. BYLVAY 120 mcg/kg/day was administered once daily. A total of 79 PFIC patients have been enrolled, of which 56 patients were rolled over from Trial 1. In addition to patients rolled over from Trial 1, an additional 23 patients were enrolled to Trial 2. Treatment-emergent adverse events were similar as observed in Trial 1. The most common reason for BYLVAY treatment interruption was liver test abnormalities (increases in ALT, AST, direct and total bilirubin). Of the 12 patients who discontinued BYLVAY in Trial 2, one patient underwent biliary diversion surgery, and a second patient received liver transplantation; both underwent surgical intervention secondary to intolerable pruritus, unresponsive to BYLVAY treatment.

7 DRUG INTERACTIONS

7.1 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 *[see Dosage and Administration (2.2)]*. Bile acid binding resins may bind odevixibat in the gut, which may reduce BYLVAY efficacy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data on BYLVAY use in pregnant persons to establish a drug-associated risk of major birth defects, miscarriage, or adverse developmental outcomes. Based on findings from animal reproduction studies, BYLVAY may cause cardiac malformations when a fetus is exposed during pregnancy. In pregnant rabbits treated orally with odevixibat during organogenesis, an increased incidence of malformations in fetal heart, great blood vessels, and other vascular sites occurred at all doses; maternal systemic exposure at the lowest dose was 2.1 times the maximum recommended dose *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, pregnant rabbits received oral doses of 10, 30, or 100 mg/kg/day during the period of organogenesis. Fetuses from all maternal groups treated with odevixibat showed an increase in cardiovascular malformations, which included 5-chambered heart, small ventricle, large atrium, ventricular septum defect, misshapen aortic valve, dilated aortic arch, right sided and retroesophageal aortic arch, fusion of aortic arch and pulmonary trunk, ductus arteriosus atresia, and absence of subclavian artery. These malformations occurred at 2.1 times the maximum recommended dose and higher, based on AUC (area under the plasma concentration-time curve). Odevixibat was shown to cross the placenta in pregnant rats.

No adverse effects on embryo-fetal development were observed following oral administration of 100, 300, or 1000 mg/kg/day in pregnant rats during organogenesis. An increase in skeletal variations (delayed/incomplete ossification and thick ribs) was observed at 1000 mg/kg/day. Maternal systemic exposure to odevixibat at the maximum dose tested was 272 times the maximum recommended dose, based on AUC.

No adverse effects on postnatal development were observed in a pre- and postnatal development study, in which female rats were treated orally with up to 1000 mg/kg/day during organogenesis through lactation. The maternal AUC for odevixibat at 1000 mg/kg/day was 434 times the maximum recommended dose, based on AUC.

8.2 Lactation

Risk Summary

Odevixibat has low absorption following oral administration, and breastfeeding is not expected to result in exposure of the infant to BYLVAY at the recommended doses *[see Clinical Pharmacology (12.3)].* There are no data on the presence of odevixibat in human milk, the effects on the breastfed infant, or the effects on milk production. BYLVAY may reduce absorption of fat-soluble vitamins *[see Warning and Precautions (5.3)]*. Monitor FSV levels and increase FSV intake, if FSV deficiency is observed during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BYLVAY and any potential adverse effects on the breastfed child from BYLVAY or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of BYLVAY have been established in pediatric patients 3 months to 17 years of age for the treatment of pruritus in PFIC. Use of BYLVAY in this age group is supported by evidence from a 24-week, randomized, double-blind, placebo-controlled trial conducted in 62 patients with a confirmed diagnosis of PFIC type 1 or type 2 (Trial 1), and an open-label 72-week extension trial in PFIC patients (Trial 2) *[see Adverse Reactions (6.1) and Clinical Studies (14)]*. Results showed a greater improvement in pruritus in patients treated with BYLVAY compared with patients treated with placebo *[see Clinical Studies (14)]*. Common reported adverse reactions in BYLVAY-treated patients from Trials 1 and 2 were liver test abnormalities, gastrointestinal symptoms (abdominal pain, vomiting and diarrhea), and fat-soluble vitamin deficiency *[see Adverse Reactions (6.1) and Warning and Precaution (5.1, 5.2, 5.3)].*

The safety and effectiveness of BYLVAY for the treatment of pruritus in PFIC in pediatric

patients less than 3 months of age have not been established.

8.5 Geriatric Use

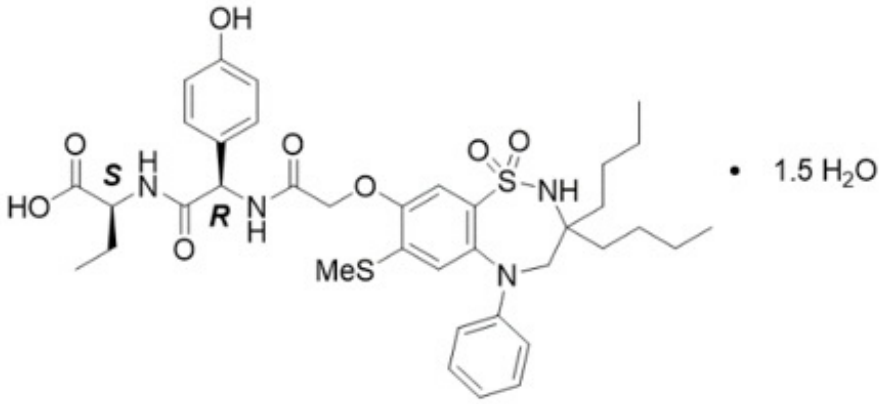
The safety and effectiveness of BYLVAY for the treatment of pruritus in PFIC in adult patients, including those 65 years of age and older, have not been established.

8.6 Hepatic Impairment

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 *[see Clinical Studies (14), Dosage and Administration (2.3), and Warning and Precautions (5.1)].*

11 DESCRIPTION

The active ingredient in BYLVAY (odevixibat) capsules and BYLVAY (odevixibat) oral pellets, an ileal bile acid transporter (IBAT) inhibitor, is (2S)-2-{[(2R)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1λ^6,2,5-benzothiadiazepin-8yl]oxy}acetamido)-2-(4-hydroxyphenyl)acetly]amino}butanoic acid, which is formulated as the sesquihydrate having the following chemical structure:



The molecular formula is $C_{37}H_{48}N_4O_8S_2 \times 1.5\ H_2O$, with a molecular weight of 768.0 g/mol (anhydrous 740.9 g/mol). Odevixibat sesquihydrate is a white to off-white solid. Its solubility in aqueous solutions is pH-dependent and increases with increased pH.

BYLVAY is available for oral administration as oral pellets containing odevixibat sesquihydrate equivalent to 200 mcg or 600 mcg of odevixibat, and as capsules containing odevixibat sesquihydrate equivalent to 400 mcg or 1200 mcg of odevixibat, and the following excipients: hypromellose and microcrystalline cellulose.

The capsule shells for the oral pellets contain hypromellose, titanium dioxide and yellow iron oxide.

The capsule shells for the capsules contain hypromellose, red iron oxide, titanium dioxide and yellow iron oxide.

The imprinting ink contains ferrosoferric oxide/black iron oxide and shellac glaze.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Odevixibat 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.

Pruritus is a common symptom in patients with PFIC and the pathophysiology of pruritus in patients with PFIC is not completely understood. Although the complete mechanism by which odevixibat improves pruritus in PFIC patients is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids *[see Clinical Pharmacology (12.2)]*.

12.2 Pharmacodynamics

Odevixibat reduces serum bile acids in patients with PFIC. In Trial 1, a 24-week, randomized, double-blind, placebo-controlled trial conducted in 62 patients with a confirmed diagnosis of PFIC type 1 or type 2, the majority of patients (88.7%) had elevated serum bile acids above 100 µmol/L at baseline *[see Clinical Studies (14)]*. Serum bile acids concentrations were reduced from baseline within 4-8 weeks of odevixibat treatment compared to placebo treatment. The decreased concentrations of serum bile acids fluctuated over time but generally were maintained during the treatment over 24 weeks. The extent of decrease in serum bile acids was similar between 40 and 120 mcg/kg.

12.3 Pharmacokinetics

In pediatric patients with PFIC, 6 months to 17 years of age who received BYLVAY 40 mcg/kg or 120 mcg/kg once daily with food in the morning, the measurable odevixibat concentrations ranged from 0.06 to 0.72 ng/mL, and odevixibat concentrations were below the limit of quantification (0.05 ng/mL) in the majority of plasma samples.

Following single and repeated oral administration of odevixibat from 0.1 to 3 mg in healthy adults, plasma concentrations of odevixibat were mostly below the limit of quantification (0.05 ng/mL); therefore, AUC and peak plasma concentration (C_{max}) could not be calculated.

Following a single administration of odevixibat 7.2 mg in healthy adults, the mean (%CV) C_{max} and $AUC_{0\text{-}24h}$ were 0.47 ng/mL (34.8) and 2.19 ng*h/mL (36.2), respectively. No accumulation of odevixibat was observed following once-daily dosing.

<u>Absorption</u>

Odevixibat is minimally absorbed following oral administration. Following a single administration of odevixibat 7.2 mg in healthy adults, odevixibat C_{max} is reached between 1 to 5 hours.

Sprinkle on Applesauce

When odevixibat 9.6 mg was administered after sprinkling the pellets on applesauce, decreases of 39% and 35% in C_{max} and $AUC_{0\text{-}24h}$, respectively, and delayed median T_{max} from 3 hours to 4.5 hours were observed compared to administration of whole capsules (eight 1200 mcg capsules) under fasted conditions. The effect of sprinkling on soft food on systemic exposure is not clinically significant *[see Dosage and*

Administration (2)].

Effect of Food

Concomitant administration of a high-fat meal (800-1000 calories with approximately 50% of total caloric content of the meal from fat) with a single dose of odevixibat 9.6 mg delayed median T_{max} from 3 hours to 4.5 hours and resulted in decreases of 72% and 62% in C_{max} and AUC_{0-24h}, respectively, compared to administration under fasted conditions in healthy adults. The effect of food on the changes of systemic exposures to odevixibat is not clinically significant *[see Dosage and Administration (2)].*

Distribution

Human plasma protein binding of odevixibat is greater than 99% in vitro.

Elimination

Following a single oral dose of 7.2 mg odevixibat in healthy adults, the mean half-life ($t_{1/2}$) was 2.36 hours.

Metabolism

In vitro, odevixibat was metabolized via mono-hydroxylation.

Excretion

Following a single radiolabeled odevixibat 3 mg oral dose in healthy adults, 82.9% of the dose was recovered in feces (97% unchanged) and less than 0.002% in the urine.

Drug Interaction Studies

Effect of Other Drugs on Odevixibat

Odevixibat is a substrate of P-glycoprotein (P-gp) but not a substrate of breast cancer resistance protein (BCRP).

Coadministration of itraconazole (a strong P-gp inhibitor) with a single dose of BYLVAY 7.2 mg increased odevixibat AUC_{0-24h} by 66% and C_{max} by 52%, which is not expected to have a clinically significant effect.

Effect of Odevixibat on Other Drugs

In in vitro studies, odevixibat was not an inhibitor of CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 nor an inducer of CYP isoforms 1A2, 2B6, or 3A4.

Concomitant use of BYLVAY 7.2 mg once daily for 4 days with oral midazolam (a CYP3A4 substrate) in healthy adults decreased the AUC_{0-24h} of midazolam and 1-OH midazolam by 29% and 13%, respectively, which is not expected to have a clinically relevant effect.

In in vitro studies, odevixibat did not inhibit the transporters P-gp; BCRP; organic anion transporter polypeptide 1B1 and 1B3(OATP1B1 and OATP1B3); organic anion transporter (OAT)1, OAT3; organic cation transporter 2 (OCT2), multidrug and toxin extrusion transporter 1 and 2K (MATE1 and MATE2K).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In 2-year carcinogenicity studies, odevixibat was not tumorigenic in rats or mice at oral doses up to 100 mg/kg/day. Systemic exposure to odevixibat (AUC) at the maximum dose studied in rats and mice was approximately 231 and 459 times the maximum recommended dose, respectively.

Mutagenesis

Odevixibat was negative in the in vitro bacterial reverse mutation (Ames) assay, the in vitro mouse lymphoma cell gene mutation assay, and the in vivo rat micronucleus test.

Impairment of Fertility

Odevixibat had no effects on fertility or reproductive function in male and female rats at oral doses of up to 1000 mg/kg/day.

14 CLINICAL STUDIES

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 m^2. 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 [*see Adverse Reactions (6)*].

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.

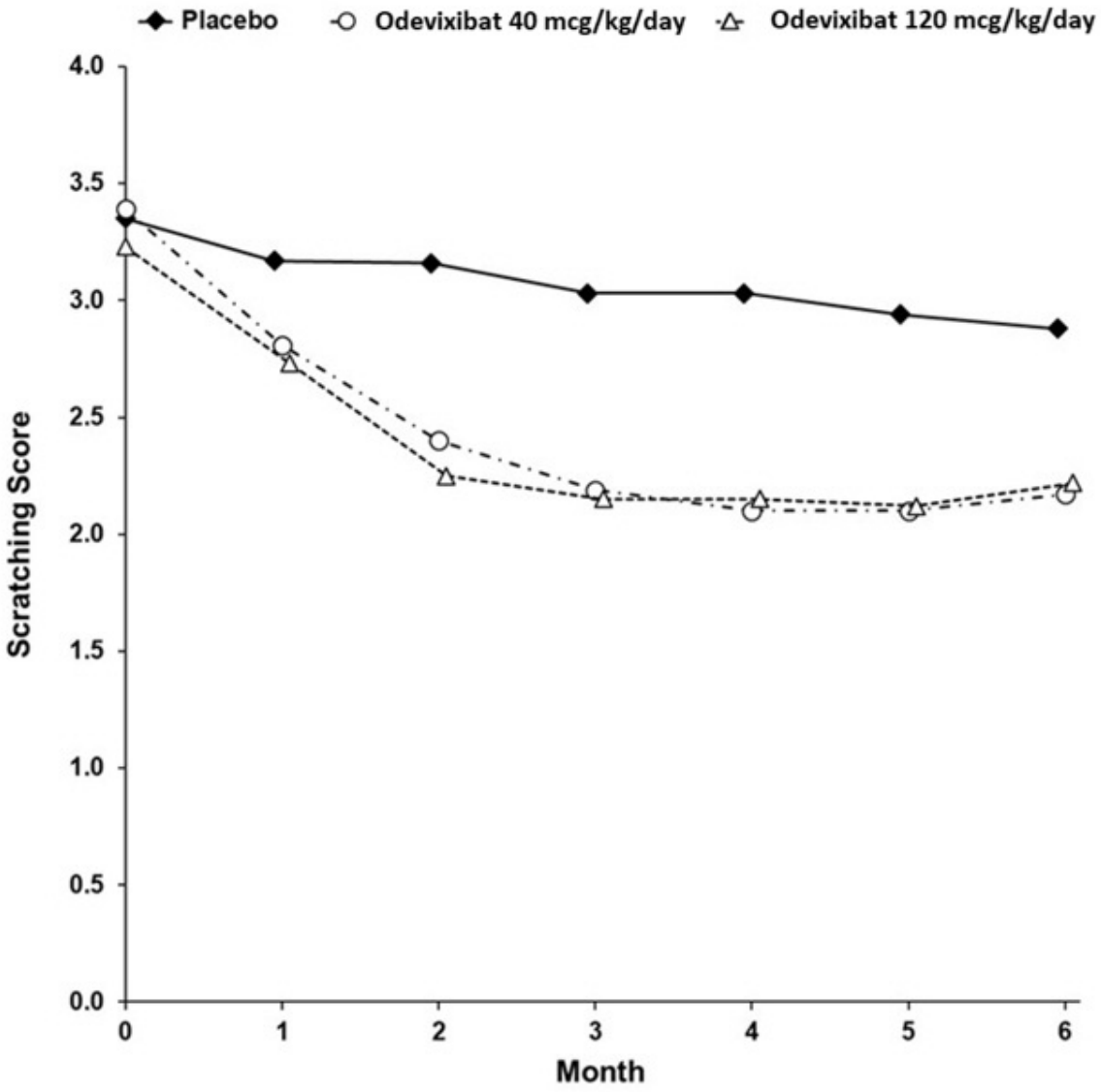
Table 4 presents the results of the comparison between BYLVAY and placebo on the mean of patients' percentage of ObsRO assessments over the 24-week treatment period that were scored as 0 (no scratching) or 1 (a little scratching). Patients treated with BYLVAY demonstrated greater improvement in pruritus 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).

Table 4: Efficacy Results Over the 24-Week Treatment Period in Patients with PFIC Type 1 or 2 in Trial 1

	Placebo (n=20)	**BYLVAY**	
		40 mcg/kg/day (n=23)	**120 mcg/kg/day (n=19)**
Mean* 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)

* 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.

Figure 1: Mean* of the Worst Weekly Average Scratching Scores for Each Month



* Figure 1 presents least squares means

Based on a mixed model repeated measure (MMRM) analysis accounting for baseline score, treatment group, time (in months), treatment-by-baseline interaction, treatment-by-time interaction, and stratification factors (i.e., PFIC type and age category). Missing data were accounted for using placebo-reference multiple imputation.

16 HOW SUPPLIED/STORAGE AND HANDLING

Oral Pellets

200 mcg Oral Pellets: supplied as Size 0 capsule with ivory opaque cap and white opaque body; imprinted "A200" (black ink). Supplied in bottles of 30 with child-resistant closure (NDC 74528-020-01).

600 mcg Oral Pellets: supplied as Size 0 capsule with ivory opaque cap and body; imprinted "A600" (black ink). Supplied in bottles of 30 with child-resistant closure (NDC 74528-060-01).

Capsules

400 mcg Capsule: supplied as Size 3 capsule with medium orange opaque cap and white

opaque body; imprinted "A400" (black ink). Supplied in bottles of 30 with child-resistant closure (NDC 74528-040-01).

1200 mcg Capsule: supplied as Size 3 capsule with medium orange opaque cap and body; imprinted "A1200" (black ink). Supplied in bottles of 30 with child-resistant closure (NDC 74528-120-01).

Storage and Handling:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Inform the patients and their caretakers of the following BYLVAY risks and oral administration procedures:

Risks

- Abdominal pain, vomiting, diarrhea, and dehydration have been reported with the use of BYLVAY. Advise patients to contact their healthcare provider if they experience new onset or worsening of diarrhea.
- Elevations in liver tests (for example, AST, ALT, TB) have been observed with use of BYLVAY. Advise patients that their healthcare provider will obtain liver tests before starting BYLVAY and periodically during treatment with BYLVAY. Advise patients to report any symptoms of liver problems (for example, nausea, vomiting, skin or the whites of eyes turn yellow, dark or brown urine, pain on the right side of the abdomen, loss of appetite).
- BYLVAY may impair absorption of fat-soluble vitamins (FSV), which include vitamins A, D, E and K (vitamin K is assessed by measuring INR). Advise patients that their healthcare provider will obtain serum levels of vitamins A, D, E, and INR (for vitamin K) at baseline and periodically during treatment to assess for worsening of FSV deficiency.

Administration

- **Do not mix BYLVAY with liquids.**
- 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 *[see Dosage and Administration (2.2)]* 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 *[see Drug Interactions (7.1)]*

Manufactured for:

Albireo Pharma, Inc.
10 Post Office Square
Boston, MA 02109

Instructions For Use
BYLVAY [bil-vay]

(odevixibat)
Capsules, for oral use
Oral Pellets

This Instructions for Use contains information on how to give BYLVAY Capsules and Oral Pellets. This information does not take the place of talking to your healthcare provider about your child's medical condition or their treatment.

Important information you need to know before giving or taking BYLVAY

- Give BYLVAY **along with the morning meal**. **Do not mix BYLVAY in liquids like breast milk, formula, or water.**
- Mix BYLVAY in a small amount of soft food (up to 2 tablespoons [30 mL]), such as apple sauce, oatmeal, banana or carrot puree, chocolate or rice pudding, in a bowl.
- **Do not** give BYLVAY to children who only take liquids (for example, breast milk, formula, or water).
- If your child is taking bile acid binding resins (for example, cholestyramine, colestipol), give them BYLVAY at least 4 hours before or 4 hours after they take the bile acid binding resin.

Preparing to Give BYLVAY

You will be provided with the number of BYLVAY Capsules or Oral Pellets prescribed by your child's healthcare provider in a child-resistant closure.

Giving BYLVAY Oral Pellets:

- The Oral Pellets are to be opened and sprinkled. **Do not** let your child swallow the capsule shell containing the Oral Pellets.
- Mix the contents of the Oral Pellets with soft food as shown in **Steps 1 through 8** below.

Step 1. Place a small amount of soft food (up to 2 tablespoons, such as apple sauce, oatmeal, banana or carrot puree, chocolate or rice pudding) in a bowl. Keep the soft food at, or cooler than, room temperature.
Note: This small amount of soft food should be less than what your child would normally eat.

Step 2. Hold the shell containing Oral Pellets horizontally on both ends, twist in opposite directions and pull apart (see **Figure A**).

Figure A

Step 3. Empty the Oral Pellets into the bowl of soft food (see **Figure B**).

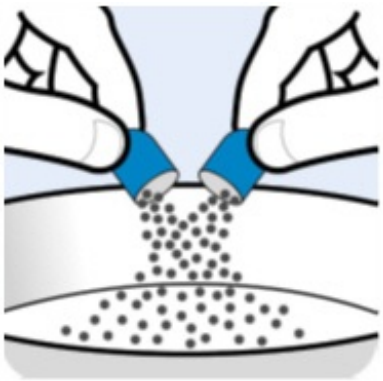


Figure B

Gently tap the shell containing Oral Pellets to make sure that all pellets come out (see **Figure C**).

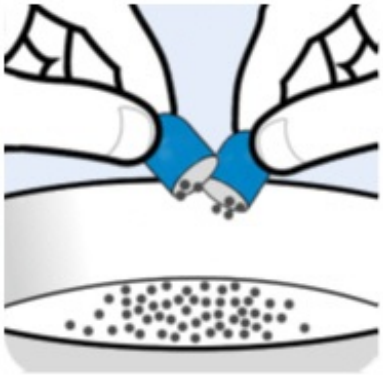


Figure C

Step 4. If the dose requires more than 1 capsule shell, repeat **Step 2** and **Step 3**.

Step 5. Gently mix the Oral Pellets with a spoon into the soft food. Please note that the Oral Pellets will not dissolve (see **Figure D**).

Figure D

Step 6. Give the entire dose right away after mixing. **Do not** store the BYLVAY mixture for later use.

Step 7. Give water after the dose is taken.

Step 8. Dispose of (throw away) the empty Oral Pellets shell(s) in the trash.

Taking BYLVAY Capsules

- Take BYLVAY Capsules **along with your morning meal**. Swallow BYLVAY Capsules whole with a glass of water. **Do not** chew or crush the Capsules.
- For children unable to swallow BYLVAY Capsules whole, follow **Steps 1 through 8** above.

How should I store BYLVAY Capsules or Oral Pellets?

Store BYLVAY at room temperature between 68°F to 77°F (20°C to 25°C).

Disposing (throwing away) of BYLVAY Capsules or Oral Pellets shells.

Dispose (throw away) the empty BYLVAY Capsule or Oral Pellets shell(s) in the household trash.

What are the ingredients in BYLVAY?

Active ingredient: odevixibat.

Inactive ingredients: hypromellose and microcrystalline cellulose.

Manufactured for:

Albireo Pharma, Inc.
10 Post Office Square
Boston, MA 02109

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Approved: July 2021

PRINCIPAL DISPLAY PANEL - 200 mcg Capsule Bottle Carton

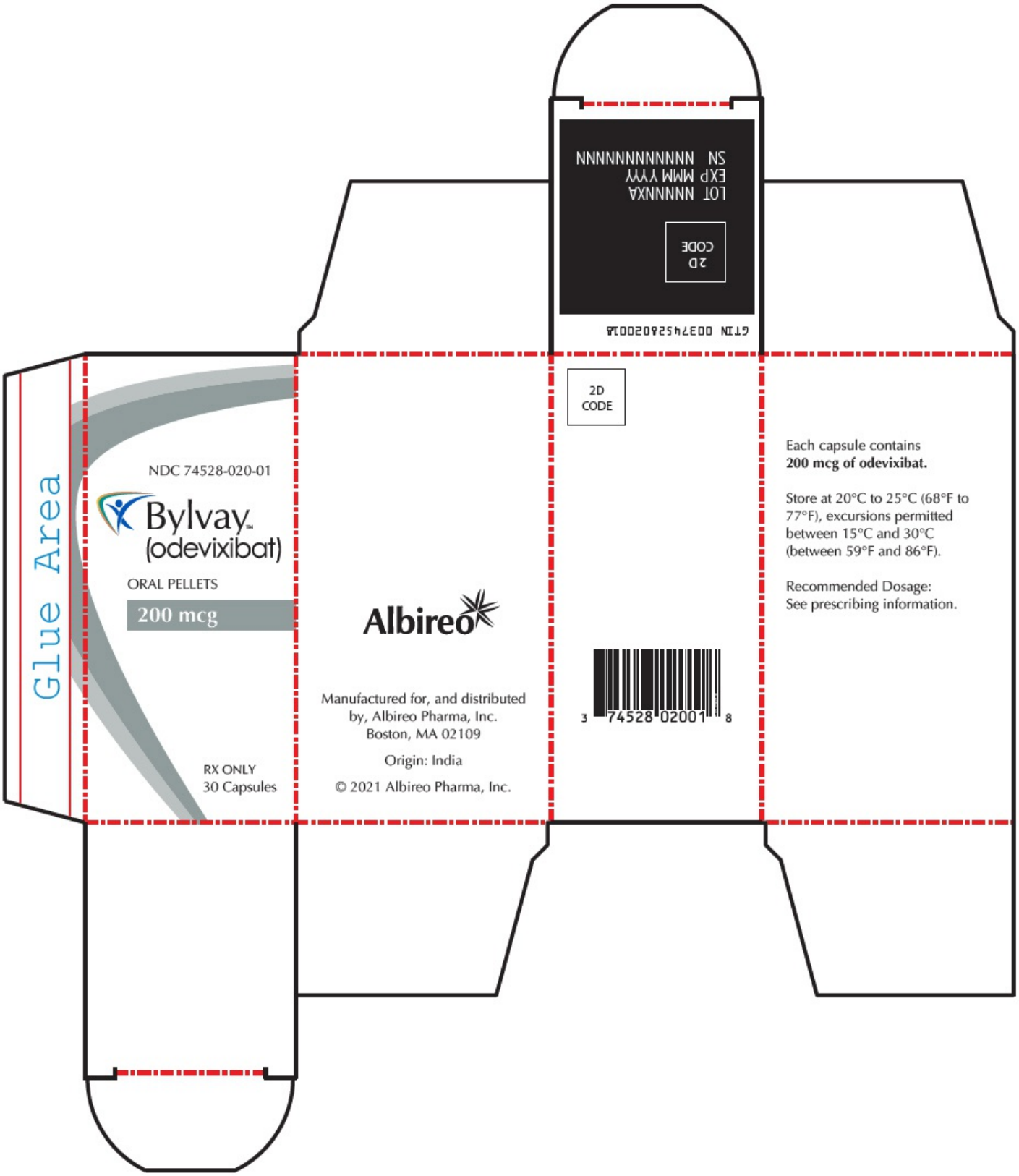
NDC 74528-020-01

Bylvay™
(odevixibat)

ORAL PELLETS

200 mcg

RX ONLY
30 Capsules



PRINCIPAL DISPLAY PANEL - 400 mcg Capsule Bottle Carton

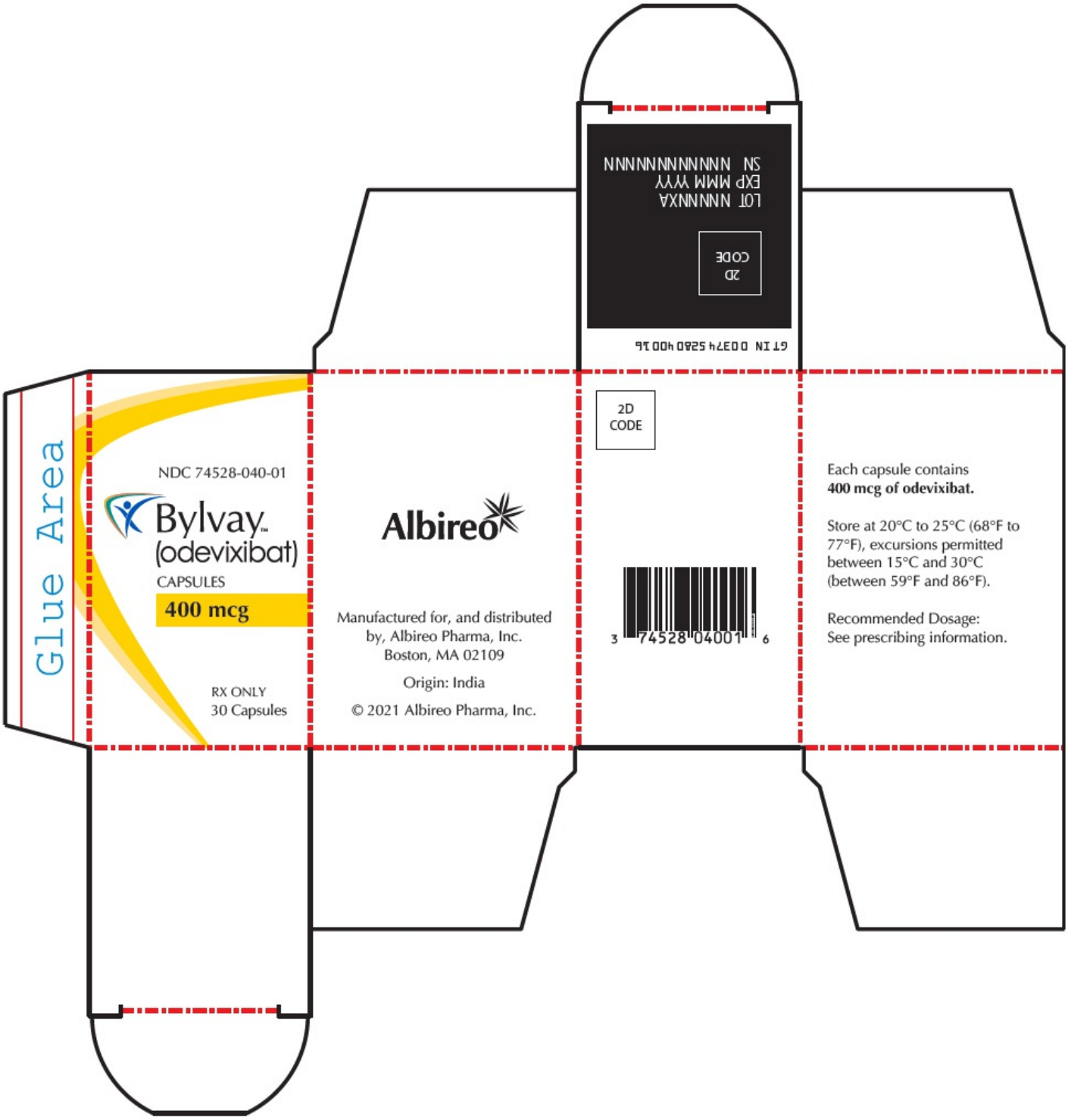
NDC 74528-040-01

Bylvay™
(odevixibat)

CAPSULES

400 mcg

RX ONLY
30 Capsules



PRINCIPAL DISPLAY PANEL - 600 mcg Capsule Bottle Carton

NDC 74528-060-01

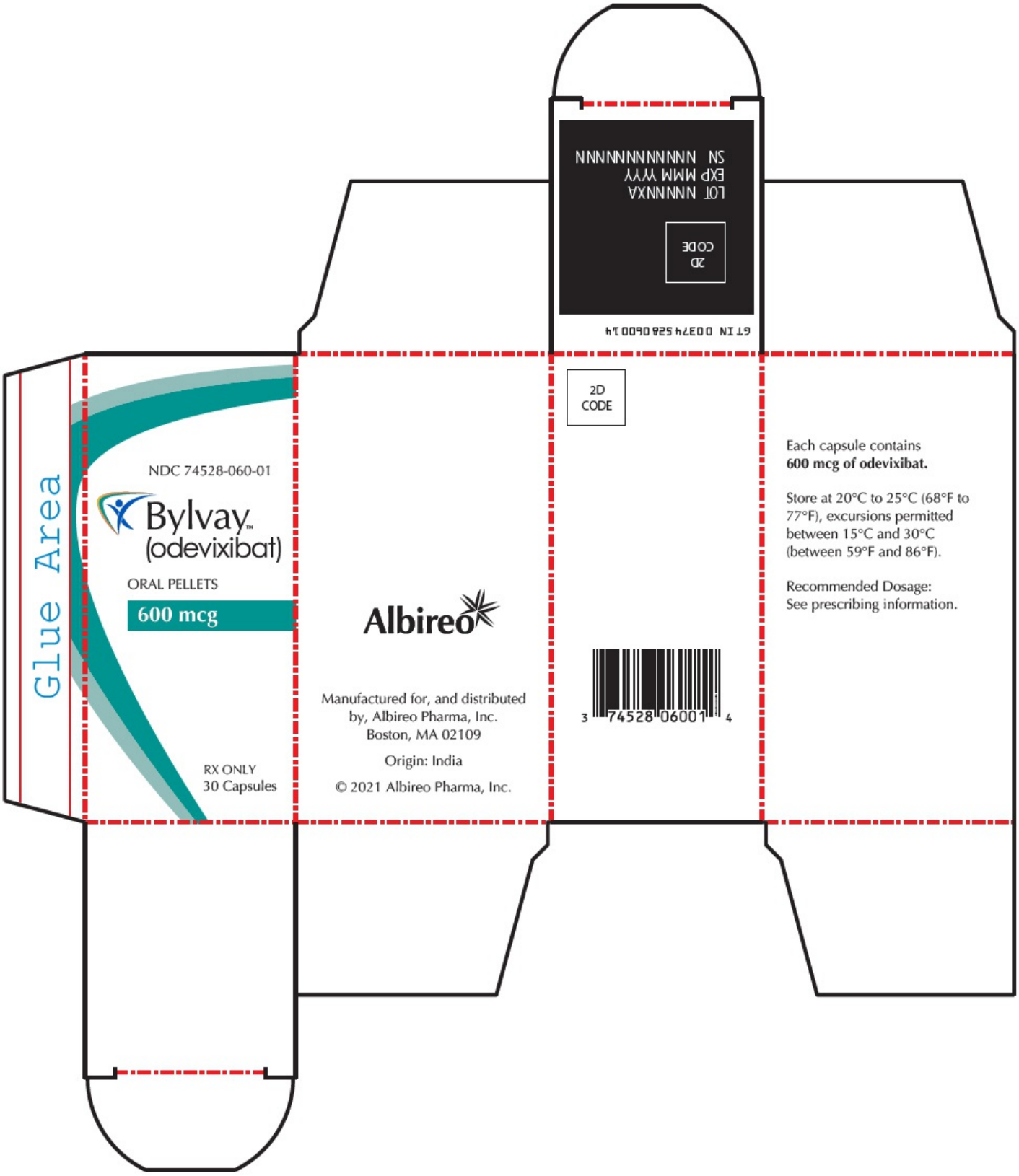
Bylvay™

(odevixibat)

ORAL PELLETS

600 mcg

RX ONLY
30 Capsules



PRINCIPAL DISPLAY PANEL - 1,200 mcg Capsule Bottle Carton

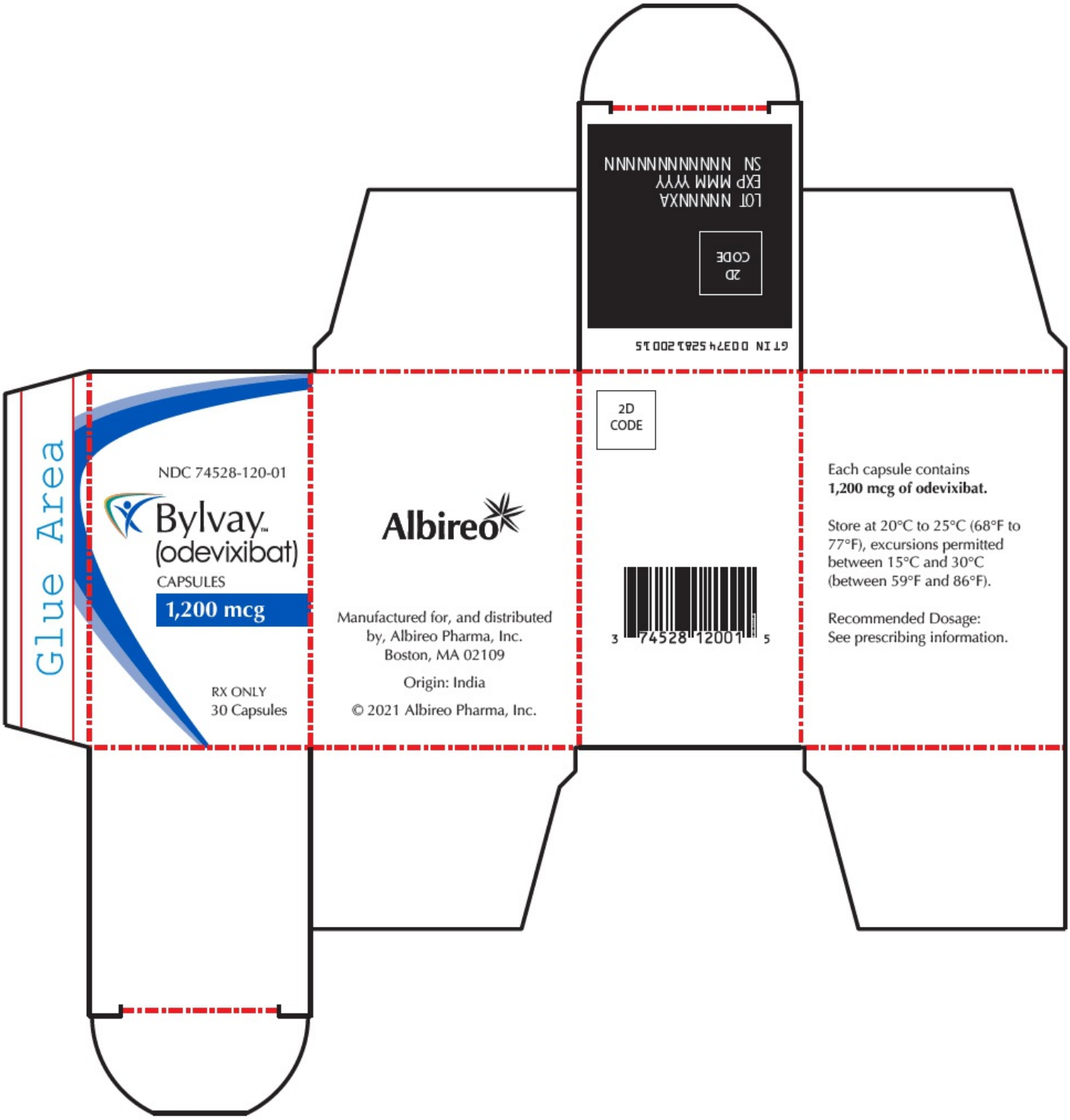
NDC 74528-120-01

Bylvay™
(odevixibat)

CAPSULES

1,200 mcg

RX ONLY
30 Capsules



BYLVAY

odevixibat capsule, coated pellets

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:74528-020
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
odevixibat (UNII: 2W150K0UUC) (odevixibat - UNII:2W150K0UUC)	odevixibat	200 ug

Inactive Ingredients

Ingredient Name	Strength
Microcrystalline cellulose (UNII: OP1R32D61U)	39 mg
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	0.8 mg

Product Characteristics

Color	WHITE (Ivory/White Opaque)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	A200
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:74528-020-01	1 in 1 CARTON	07/20/2021	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA215498	07/20/2021	

BYLVAY

odevixibat capsule, coated pellets

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:74528-040
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
odevixibat (UNII: 2W150K0UUC) (odevixibat - UNII:2W150K0UUC)	odevixibat	400 ug

Inactive Ingredients

Ingredient Name	Strength
Microcrystalline cellulose (UNII: OP1R32D61U)	78 mg
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	1.6 mg

Product Characteristics

Color	ORANGE (Medium Orange Opaque/White Opaque)	**Score**	no score
Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	A400
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:74528-040-01	1 in 1 CARTON	07/20/2021	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA215498	07/20/2021	

BYLVAY

odevixibat capsule, coated pellets

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:74528-060
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
odevixibat (UNII: 2W150K0UUC) (odevixibat - UNII:2W150K0UUC)	odevixibat	600 ug

Inactive Ingredients

Ingredient Name	Strength

Microcrystalline cellulose (UNII: OP1R32D61U)	37 mg
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	2.4 mg

Product Characteristics

Color	WHITE (Ivory Opaque)	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	A600
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:74528-060-01	1 in 1 CARTON	07/20/2021	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA215498	07/20/2021	

BYLVAY

odevixibat capsule, coated pellets

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:74528-120
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
odevixibat (UNII: 2W150K0UUC) (odevixibat - UNII:2W150K0UUC)	odevixibat	1200 ug

Inactive Ingredients

Ingredient Name	Strength
Microcrystalline cellulose (UNII: OP1R32D61U)	74 mg
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	4.8 mg

Product Characteristics

Color	ORANGE (Medium Orange Opaque)	**Score**	no score

Shape	CAPSULE	**Size**	16mm
Flavor		**Imprint Code**	A1200
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:74528-120-01	1 in 1 CARTON	07/20/2021	
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA215498	07/20/2021	

Labeler - Albireo Pharma, Inc. (145773359)

Revised: 7/2021 Albireo Pharma, Inc.