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

----------RECENT MAJOR CHANGES----------

Contraindications (4)	3/2025
Warnings and Precautions (5.1, 5.3)	3/2025

----------INDICATIONS AND USAGE----------

BYLVAY is an ileal bile acid transporter (IBAT) inhibitor indicated for:

Progressive Familial Intrahepatic Cholestasis (PFIC)

- the treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC). (1.1)

Limitation 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 the bile salt export pump protein. (1.1, 12.5, 14)

Alagille Syndrome (ALGS)

- the treatment of cholestatic pruritus in patients 12 months of age and older with Alagille syndrome (ALGS). (1.2)

----------DOSAGE AND ADMINISTRATION----------

Recommended Dosage
PFIC:

- Patients 3 months and older: 40 mcg/kg taken orally once daily. (2.1)
- 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 daily dosage of 6 mg/day. (2.1)

ALGS:

- Patients 12 months and older: 120 mcg/kg taken orally once daily. (2.2)
- Preparation and Administration Instructions
  - Administer BYLVAY in the morning with a meal. (2.4)
  - Do not crush or chew capsules. (2.4)
  - See full prescribing information for preparation and administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

Patients with prior or active hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatoxicity: Obtain baseline liver tests and monitor patients frequently for the first 6 to 8 months after starting therapy, and as clinically indicated thereafter during treatment. If liver test abnormalities or signs of clinical hepatitis occur, consider dose reduction or treatment interruption. For persistent or recurrent liver test abnormalities relative to baseline, discontinue BYLVAY. Monitor patients with compensated cirrhosis or portal hypertension more frequently. Permanently discontinue BYLVAY if hepatic decompensation occurs. (2.3, 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 with FSV if deficiency is observed. If FSV deficiency persists or worsens despite FSV supplementation, consider permanent discontinuation of treatment. Interrupt treatment with BYLVAY if bleeding occurs. Optimize treatment of FSV deficiency and consider restarting BYLVAY once the patient is clinically stable. (5.3)

----------ADVERSE REACTIONS----------

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

ALGS: Most common adverse reactions (>5%) are diarrhea, abdominal pain, hematoma, and decreased weight. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 1-855-463-5127, 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 and FDA-approved patient labeling.

Revised: 3/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Progressive Familial Intrahepatic Cholestasis (PFIC)

BYLVAY is indicated for the treatment of pruritus in patients 3 months of age and older with PFIC.

Limitations 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 the bile salt export pump protein *[see Clinical Pharmacology (12.5) and Clinical Studies (14)]*.

1.2 Alagille Syndrome (ALGS)

BYLVAY is indicated for the treatment of cholestatic pruritus in patients 12 months of age and older with ALGS.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Progressive Familial Intrahepatic Cholestasis (PFIC) in Patients Aged 3 Months and Older

- The recommended dosage of BYLVAY is 40 mcg/kg taken orally once daily in the morning with a meal. Table 1 below shows the recommended once daily dosage by body weight.

- 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 daily dosage of 6 mg/day.

- 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 PFIC in Patients aged 3 months and older (40 mcg/kg/day)

Body Weight (kg)	Once Daily Dosage (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	1,200
35.5 to 45.4	1,600
45.5 to 55.4	2,000
55.5 and above	2,400

2.2 Recommended Dosage for Alagille Syndrome (ALGS) in Patients Aged 12 Months and Older

- The recommended dosage of BYLVAY is 120 mcg/kg taken orally once daily in the morning with a meal. Table 2 below shows the recommended once daily dosage by body weight.

- 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 2. Recommended Dosage for ALGS in Patients aged 12 months and older (120 mcg/kg/day)

Body Weight (kg)	Once Daily Dosage (mcg)
7.4 and below	600
7.5 to 12.4	1,200
12.5 to 17.4	1,800
17.5 to 25.4	2,400
25.5 to 35.4	3,600
35.5 to 45.4	4,800
45.5 to 55.4	6,000
55.5 and above	7,200

2.3 Dosage Modification for Management of Adverse Reactions

Tolerability for Alagille Syndrome (ALGS)

Dose reduction to 40 mcg/kg/day (Table 1) may be considered if tolerability issues occur in the absence of other causes. Once tolerability issues stabilize, increase to 120 mcg/kg/day.

Liver Test Abnormalities

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 recommended dosage *[see Dosage and Administration (2.1, 2.2)]*. 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).

2.4 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 Pellets into soft food or a liquid (as described below).
  - Discard the emptied shells. Do not let your child swallow the unopened shells containing the Oral Pellets.

Administration Instructions for patients capable of swallowing soft food:

1. Administer BYLVAY with the first morning meal.
2. Place a small amount (up to 2 tablespoons [30 mL]) of soft food (apple sauce, oatmeal, banana or carrot puree, chocolate or rice pudding) in a bowl. Keep the soft food at, or cooler than, room temperature.
3. Open the shell containing 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.
4. If the dose requires more than one shell of Oral Pellets, repeat Step 3.
5. Gently mix until well dispersed and administer the entire dose immediately.
6. Follow the dose with breast milk, infant formula, or other age-appropriate liquid.
7. Do not store the mixture for future use.
8. For patients unable to swallow soft food, see the instructions below.

Administration Instructions with liquids (Using an oral dosing syringe):

1. Administer BYLVAY with the first morning meal.
2. Open the shell containing Oral Pellets and empty the contents into a small mixing cup. Gently tap the shell containing Oral Pellets to ensure that all contents have been emptied into the mixing cup.
3. If the dose requires more than one shell of Oral Pellets, repeat Step 2.
4. Add 1 teaspoon (5 mL) of an age-appropriate liquid (for example, breast milk, infant formula, or water).
5. Let the pellets sit in the liquid for approximately 5 minutes to allow complete wetting REMINDER: The Oral Pellets will not dissolve in the liquid.
6. After 5 minutes, place the tip of the oral syringe completely into the mixing cup. Pull the plunger of the syringe up slowly to withdraw the liquid/pellet mixture into the syringe. Gently push the plunger down again to expel the liquid/pellet mixture back into the mixing cup. Do this 2 to 3 times to ensure complete mixing of the pellets into the liquid.
7. Withdraw the entire contents into the oral syringe by pulling the plunger on the end of the syringe.
8. Place the tip of the syringe into the front of the patient’s mouth between the tongue and the side of the mouth, and then gently push the plunger down to squirt the liquid/pellet mixture between your child's tongue and the side of the mouth. Do not squirt liquid/pellet mixture in the back of the child's throat because this could cause gagging or choking.
9. Do not administer via a bottle or “sippy cup” because the Oral Pellets will not pass through the opening. The oral pellets will not dissolve in liquid.
10. Follow the dose with breast milk, infant formula, or other age-appropriate liquid.
11. If any pellet/liquid mixture remains in the mixing cup, repeat Step 7 and Step 8 until the entire dose has been administered.
12. Check the child's mouth to make sure all of the liquid/pellet mixture has been swallowed.

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, or mixed with an age-appropriate liquid. Follow directions above for oral pellets to prepare and administer such a mixture.

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

IBAT inhibitors, including BYLVAY, are contraindicated in patients with prior or active hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy) *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatoxicity

BYLVAY treatment is associated with a potential for drug-induced liver injury (DILI).

In the PFIC and ALGS trials, treatment-emergent elevations of liver tests or worsening of liver tests occurred. Of the six patients who experienced DILI, two underwent liver transplant.

Obtain baseline liver tests because some ALGS and PFIC patients have abnormal liver tests at baseline. Monitor patients frequently for the first 6 to 8 months after starting therapy and as clinically indicated thereafter during treatment with BYLVAY. Monitor for elevation in liver tests, for the development of liver-related adverse reactions, and for physical signs of hepatic decompensation. If liver test abnormalities or signs of clinical hepatitis occur in the absence of other causes, consider dose reduction or treatment interruption.

Permanently discontinue BYLVAY if a patient experiences the following:
- persistent or recurrent liver test abnormalities, or
- upon rechallenge, signs and symptoms consistent with clinical hepatitis, or
- a hepatic decompensation event.

The safety and effectiveness of BYLVAY have not been established in patients with decompensated cirrhosis. Monitor patients with compensated cirrhosis or portal hypertension more frequently and discontinue BYLVAY if hepatic decompensation occurs. IBAT inhibitors, including BYLVAY, are contraindicated in patients with prior or active hepatic decompensation

events *[see Contraindications (4)]*.

5.2 Diarrhea

In Trial 1, diarrhea in PFIC patients 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.

In Trial 3, diarrhea in ALGS patients was reported in 1 placebo-treated patient (6%) and in 10 (29%) BYLVAY-treated patients *[see Adverse Reactions (6.1)]*. No patients interrupted or permanently discontinued BYLVAY due to 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 Deficiency

BYLVAY may adversely affect absorption of fat-soluble vitamins (FSV). FSV include vitamin A, D, E, and K (measured using INR levels). PFIC and ALGS patients can have FSV deficiency at baseline and are frequently supplemented with FSV.

In Trial 1 in PFIC patients, 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 patients treated with BYLVAY dosage 40 mcg/kg/day had new onset or worsening of existing FSV deficiency.

In Trial 3 in ALGS patients, new or worsening of existing FSV deficiency was reported in 3 (17.6%) placebo- treated patients and 3 (8.6%) BYLVAY-treated patients *[see Adverse Reactions (6.1)]*.

Obtain serum FSV levels at baseline and monitor during treatment, along with any clinical manifestations of FSV deficiency. If FSV deficiency is diagnosed, supplement with FSV. If FSV deficiency persists or worsens despite adequate FSV supplementation, consider permanent discontinuation of BYLVAY depending on the benefit and risk balance.

If complications of FSV deficiency occur, consider interrupting BYLVAY treatment and reassess to ensure adequate supplementation with FSV. Consider restarting BYLVAY once the patient is clinically stable.

Bleeding

Interrupt treatment with BYLVAY if bleeding occurs. Optimize treatment of FSV deficiency and consider restarting BYLVAY once the patient is clinically stable.

6 ADVERSE REACTIONS

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

- Hepatotoxicity [*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.

PFIC Clinical Studies

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 *[see Clinical Studies (14.1)]*. 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 adverse reactions reported in ≥2% and at a rate greater than placebo in patients treated with BYLVAY in Trial 1. The most common adverse reactions observed in Trial 1 included diarrhea, liver test abnormalities, vomiting, abdominal pain, and fat-soluble vitamin deficiency.

Table 3. Common Adverse Reactions[a] from a Clinical Study of BYLVAY in Patients with Progressive Familial Intrahepatic Cholestasis (Trial 1)

Adverse Reaction	Placebo N=20 n (%)	BYLVAY 40 mcg/kg/day N=23 n (%)	BYLVAY 120 mcg/kg/day N=19 n (%)
Diarrhea	2 (10%)	9 (39%)	4 (21%)
Transaminases increased (ALT, AST)	1 (5%)	3 (13%)	4 (21%)
Vomiting	0	4 (17%)	3 (16%)
Abdominal pain	0	3 (13%)	3 (16%)
Blood bilirubin increased	2 (10%)	3 (13%)	2 (11%)
Fat-soluble vitamin deficiency (A, D, E)	1 (5%)	0	3 (16%)
Splenomegaly	0	0	2 (11%)
Cholelithiasis	0	0	1 (5%)
Dehydration	0	0	1 (5%)
Fracture	0	1 (4%)	0

[a] Adverse reactions that occurred in ≥2% of BYLVAY-treated patients

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 26 years. BYLVAY 120 mcg/kg/day was administered once daily. A total of 116 PFIC patients were enrolled, of which 56 patients were rolled over from Trial 1. In addition to patients rolled over from Trial 1, an additional 60 patients were enrolled to Trial 2. Treatment-emergent adverse reactions were similar as observed in Trial 1. Adverse reactions observed in Trial 2 but not described in Trial 1 (Table 3) included increased INR (16%), epistaxis (9%), coagulopathy (3%), iron deficiency anemia (3%), prolonged prothrombin time (2%) and variceal hemorrhage, stoma hemorrhage, hematochezia, and rectal hemorrhage (<1% each). The most common reason for

BYLVAY treatment interruption was liver test abnormalities (increases in ALT, AST, direct and total bilirubin).

Of the 33 patients who discontinued BYLVAY in Trial 2, five underwent or were referred for liver transplantation and one patient underwent surgical biliary diversion (SBD). There were a total of 19 patients who underwent surgical intervention in Trial 2, with one patient who had SBD followed by liver transplant, 15 patients who underwent liver transplant alone, and three patients who underwent SBD alone.

ALGS Clinical Studies

Trial 3 is a randomized, double-blind, placebo-controlled, 24-week study of a single dose level of BYLVAY (120 mcg/kg) administered once daily *[see Clinical Studies (14.2)]*. Fifty-two patients were randomized (2:1) to receive one of the following:

- BYLVAY 120 mcg/kg/day (n=35), or
- Placebo (n=17).

Table 4 summarizes the frequency of adverse reactions in patients with ALGS, reported in ≥5% and at a rate greater than placebo in patients treated with BYLVAY in Trial 3. No patients discontinued study treatment due to an adverse reaction. The most common adverse reactions observed in Trial 3 included diarrhea, abdominal pain, hematoma, and decreased weight.

Table 4. Common Adverse Reactions[a] from a Clinical Study of BYLVAY in Patients with Alagille Syndrome (Trial 3)

Adverse Reaction	Placebo N=17 n (%)	BYLVAY 120 mcg/kg/day N=35 n (%)
Diarrhea	1 (6%)	10 (29%)
Abdominal Pain	1 (6%)	5 (14%)
Hematoma	0	3 (9%)
Weight decreased	0	2 (6%)

[a] Adverse reactions that occurred in ≥5% of BYLVAY-treated patients

Trial 4 is a 72-week, open-label extension study in 49 pediatric patients with ALGS aged 1 to 15 years. BYLVAY 120 mcg/kg/day was administered once daily. Treatment-emergent adverse reactions were similar to those observed in Trial 3. The most common reason for BYLVAY treatment interruption was gastrointestinal disorders, including diarrhea and abdominal pain.

Hepatotoxicity

BYLVAY treatment is associated with a potential for DILI.

In the PFIC and ALGS trials, treatment-emergent elevations of liver tests or worsening of liver tests occurred. Of the six patients who experienced DILI, two underwent liver transplant.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BYLVAY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: gastrointestinal hemorrhage, gingival hemorrhage, liver transplant

Investigations: gamma-glutamyltransferase increased, hemoglobin decreased

Nervous system disorders: extra-axial hemorrhage (subdural hemorrhage)

Respiratory, thoracic, and mediastinal disorders: epistaxis

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 (2.3)]*. 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.

There is a pregnancy safety study that monitors pregnancy outcomes in women exposed to BYLVAY during pregnancy. Pregnant women exposed to BYLVAY, or their healthcare providers, should report BYLVAY exposure by calling 1-855-463-5127.

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 1,000 mg/kg/day in pregnant rats during organogenesis. An increase in skeletal variations (delayed/incomplete ossification and thick ribs) was observed at 1,000 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 1,000 mg/kg/day during organogenesis through lactation. The maternal AUC for odevixibat at 1,000 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 one 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 extension trial in PFIC patients (Trial 2) *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

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.

The safety and effectiveness of BYLVAY have been established in pediatric patients 12 months to 17 years of age for the treatment of pruritus in ALGS. Use of BYLVAY in this age group is supported by evidence from one randomized, double-blind, placebo-controlled trial conducted in 52 patients with a confirmed diagnosis of ALGS (Trial 3) and one open-label extension trial in ALGS patients (Trial 4) *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

The safety and effectiveness of BYLVAY for the treatment of pruritus in ALGS in pediatric patients less than 12 months of age have not been established.

8.5 Geriatric Use

PFIC and ALGS are largely diseases of pediatric and young adult patients. Clinical studies in BYLVAY did not include patients 65 years of age and older.

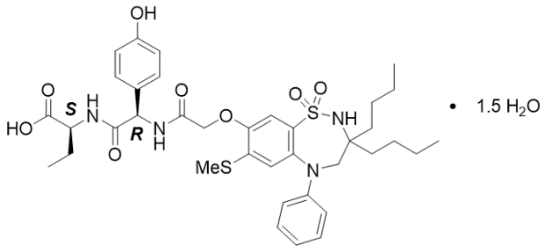
8.6 Hepatic Impairment

Patients with PFIC and ALGS may have impaired hepatic function. The efficacy and safety of BYLVAY in PFIC and ALGS patients with clinically significant portal hypertension, and in patients with

decompensated cirrhosis have not been established *[see Dosage and Administration (2.3), Contraindications (4), Warning and Precautions (5.1), and Clinical Studies (14)].*

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 $C_{37}H_{48}N_4O_8S_2$ x 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 ALGS; the pathophysiology of pruritus in patients with PFIC is not completely understood. Although the complete mechanism by which odevixibat improves pruritus in both PFIC and ALGS 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 and ALGS.

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 mcmol/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.

Trial 3 is a 24-week, randomized, double-blind, placebo-controlled trial conducted in 52 patients with a confirmed diagnosis of ALGS who were administered treatment with BYLVAY 120 mcg/kg once daily *[see Clinical Studies (14)].* At baseline, serum bile acids were variable ranging from 93 to 510 mcmol/L. Serum bile acid concentrations were reduced from baseline as early as Week 4 of odevixibat treatment and the reduction was generally maintained during treatment over 24 weeks.

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.

In pediatric patients with ALGS who received BYLVAY 120 mcg/kg once daily with food in the morning, the measurable odevixibat concentrations ranged from 0.05 to 3.4 ng/mL.

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.

Absorption

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 (2.3)].*

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 $AUC_{0\text{-}24h}$, 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 (2.3)].*

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 $AUC_{0\text{-}24h}$ 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 $AUC_{0\text{-}24h}$ 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).

12.5 Pharmacogenomics

PFIC is a heterogenous disease caused by homozygous or compound heterozygous variants, with different PFIC subtypes occurring in the general population. PFIC2 is the most common subtype accounting for 37-90% of PFIC patients. PFIC1 is caused by variants in the aminophospholipid flippase (ATP8B1) gene, which encodes the Familial Intrahepatic Cholestasis 1 (FIC1) protein, while

PFIC2 results from variants in the ABCB11 gene, which encodes the Bile Salt Export Pump (BSEP) protein. PFIC2 patients are further categorized into BSEP subgroups based on their specific variants. The BSEP-1 subgroup includes patients with at least one p.D482G (c.1445A>G) or p.E297G (c.890A>G) variant, BSEP-2 includes patients with at least one missense variant other than p.D482G or p.E297G (non BSEP-1), and BSEP-3 includes patients with variants that are predicted to encode a non-functional protein. No BSEP-3 patients were studied in clinical Trial 1 (NCT03566238). The prevalence of BSEP-1, BSEP-2, and BSEP-3 subgroups are approximately 27.3%, 51.5%, and 21.2%, respectively, based on data from a global consortium characterizing the natural history of severe BSEP deficiency.

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 1,000 mg/kg/day.

14 CLINICAL STUDIES

14.1 PFIC

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 reaction of diarrhea *[see Adverse Reactions (6)].*

Given the patients' young age, a single-item observer-reported outcome (ObsRO) was used to measure patients' scratching severity as observed by their caregiver twice daily (once in the morning and once in the evening). Scratching severity 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 their average scratching score was greater than or equal to 2 (medium scratching) in the 2 weeks prior to baseline.

Table 5 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 5: 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[a] 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)

[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.

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

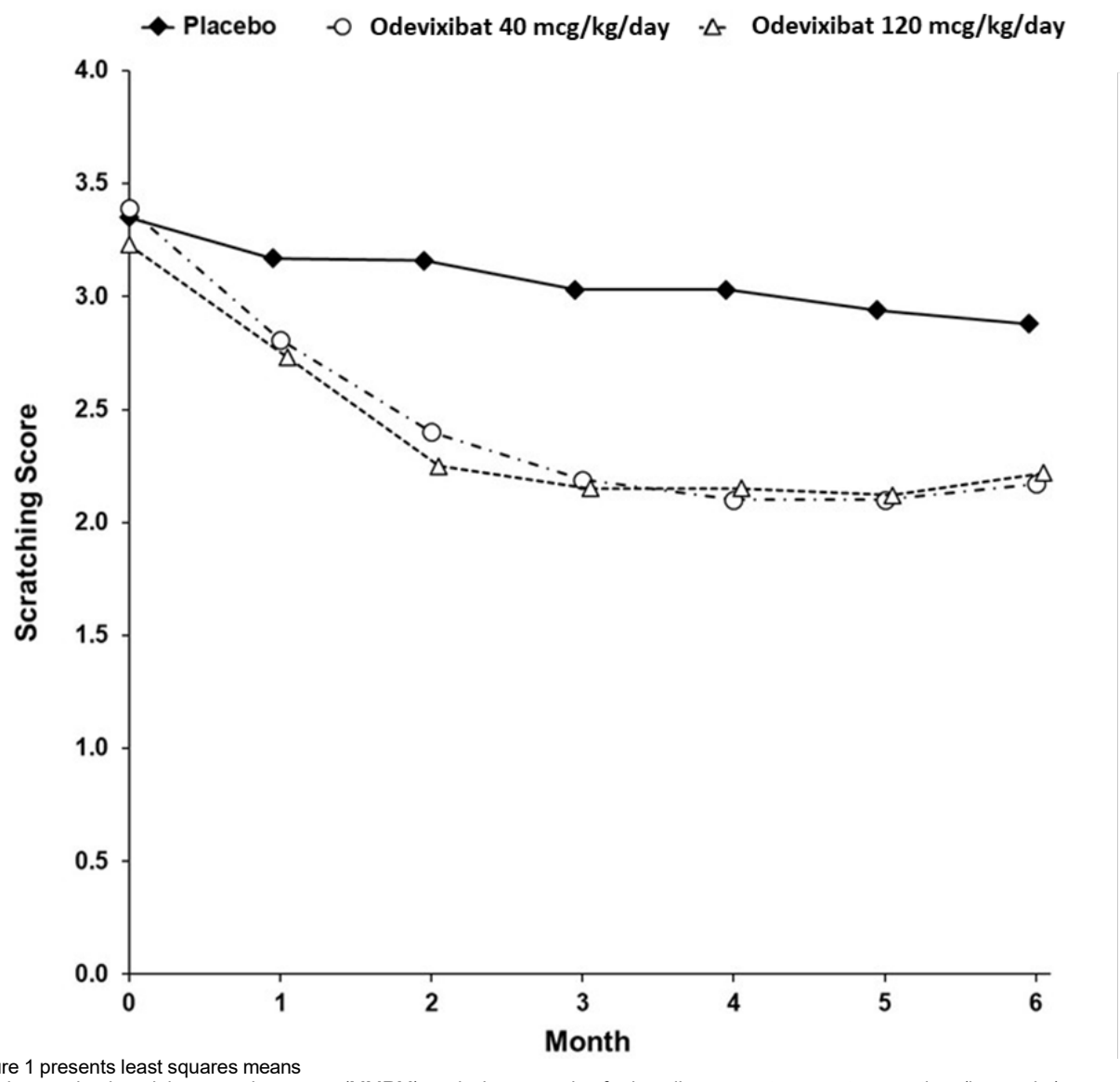


*Figure 1 presents least squares means
Based on a mixed model repeated measure (MMRM) analysis accounting for baseline score, treatment group, time (in months), treatment-by-baseline interaction, treatment-by-time interaction, and stratification factors (i.e., PFIC type and age category). Missing data were accounted for using placebo-reference multiple imputation.

14.2 ALGS

The efficacy of BYLVAY was evaluated in Trial 3 (NCT04674761), a 24-week, randomized, double-blind, placebo-controlled trial. Trial 3 was conducted in 52 pediatric patients, aged 6 months to 15 years, with a confirmed diagnosis of ALGS and presence of pruritus at baseline. Patients who had decompensated liver disease, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT was greater than 10-times the upper limit of normal (ULN) at screening, whose total bilirubin was greater than 15-times the ULN at screening, or who had received a liver transplant were excluded from Trial 3.

Patients were randomized to placebo (n=17) or 120 mcg/kg (n=35). 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 3 was 6.1 (1.7 to 15.5) years in the BYLVAY group and 4.2 (0.5 to 14.3) years in the placebo group; 5 patients were older than 12 years of age. Of the 52 patients, 52% were male and 83% were white; 92% of patients had the JAG1 mutation and 8% had the NOTCH2 mutation. The mean (standard deviation [SD]) scratching score in the 2 weeks prior to baseline was 2.9 (0.6). Baseline mean (SD) eGFR was 159 (51.4) mL/min/1.73 m^2. Baseline median (range) ALT, AST, and total bilirubin were 152 (39-403) U/L, 135 (57-427) U/L, and 2.0 (0.4-11.4) mg/dL, respectively.

Given the patients' young ages, a single-item observer-reported outcome (ObsRO) was used to measure patients' scratching severity as observed by their caregiver twice daily (once in the morning and once in the evening). Scratching severity 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 3 if the average scratching score was greater than or equal to 2 (medium scratching) in the 14 days prior to baseline.

Table 6 presents the results of the comparison between BYLVAY and placebo on the change from baseline in average scratching score based on ObsRO assessments to Month 6 (Weeks 21 to 24). The average scratching score for each patient for each month post-baseline was calculated by: (Step 1) averaging the morning scores and averaging the evening scores within a week; (Step 2) averaging the morning and evening weekly scores to yield a single weekly score; and finally (Step 3) averaging the 4 weekly scores within the month. The baseline average scratching score for each patient was calculated by averaging the weekly scores obtained in Step 2 across the 2 weeks prior to randomization and initiation of blinded treatment. Patients treated with BYLVAY demonstrated greater improvement in pruritus compared with placebo. Figure 2 displays the means (95% confidence interval) of patients' average scratching scores in each treatment group for each month.

Table 6: Efficacy Results in Patients with ALGS in Trial 3

	Placebo (n=17)	**BYLVAY 120 mcg/kg/day (n=35)**
Baseline Average Scratching Score		
Mean (SD)	3.0 (0.6)	2.8 (0.5)
Change from Baseline in Average Scratching Score to Month 6 (Weeks 21 to 24)[a]		
Mean (SE)	-0.8 (0.2)	-1.7 (0.2)
Mean Difference vs Placebo (95% CI) p-value	-0.9 (-1.4, -0.3) 0.002	

[a] Based on least square means from a mixed-effect model for repeated measures (MMRM) for change from baseline to each month accounting for baseline average scratching score, baseline age stratification (<10, ≥10 years), baseline direct bilirubin, treatment group, time (in months), and treatment-by-time interaction.

Figure 2: Mean* of the Average Scratching Scores for Each Month in Trial 3

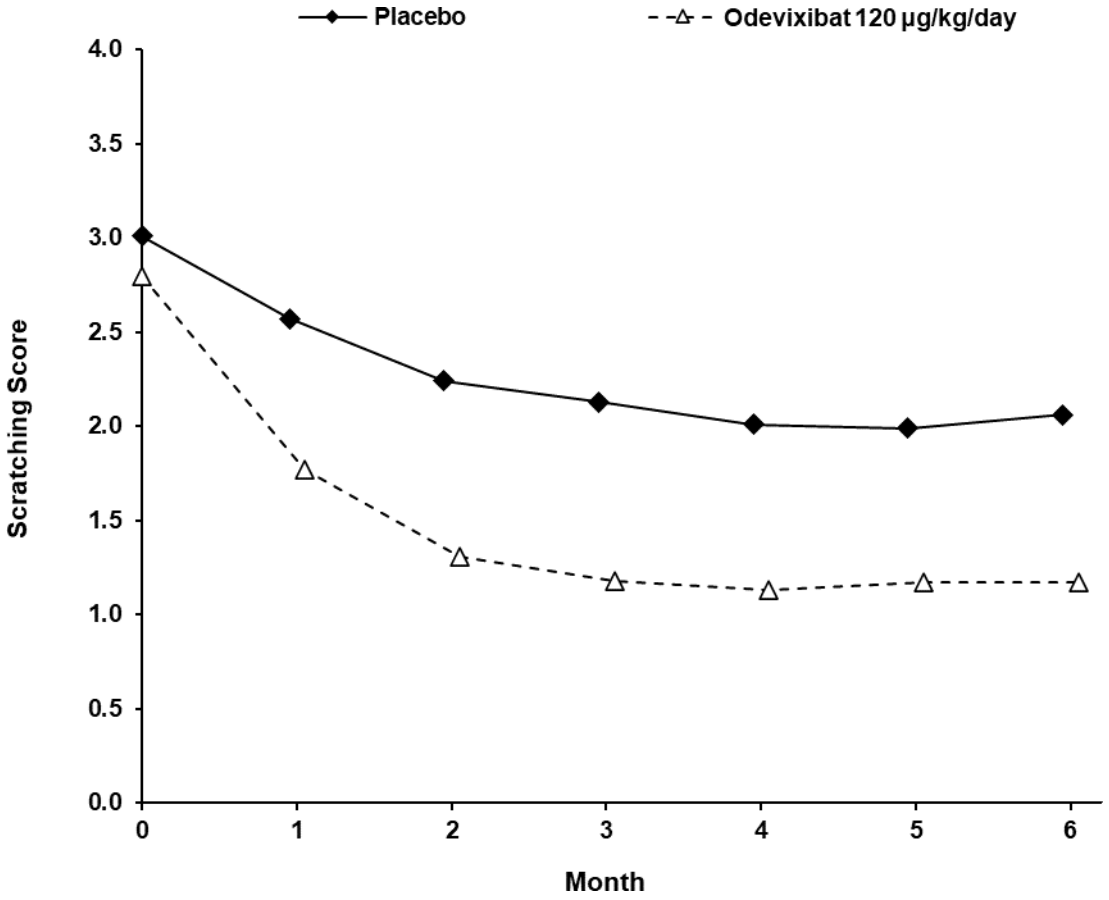


*Figure 2 presents means for baseline and least squares means for Month 1 to 6
Least squares means are based on a mixed model repeated measure (MMRM) analysis accounting for baseline average scratching score, baseline age stratification (<10, ≥10 years), baseline direct bilirubin, treatment group, time (in months), and treatment-by-time interaction.

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 (NDC15054-3301-1).

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 (NDC15054-3303-1).

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 (NDC15054-3302-1).

1,200 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 15054-3304-1).

Storage and Handling:

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Administration Instructions

Advise patients or their caregivers(s) to:

- Take BYLVAY in the morning with a meal. 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 or liquids *[see Dosage and Administration (2.1, 2.2, 2.4)]*.
- Follow stepwise administration Instructions *[see Dosage and Administration (2.4)]* for Oral Pellets and Capsules for patients unable to swallow the capsules whole.
- Take BYLVAY at least 4 hours before or 4 hours after taking a bile acid binding resin (e.g., cholestyramine, colesevelam, or colestipol) *[see Drug Interactions (7.1)].*

Hepatotoxicity

Advise patients or their caregiver(s) that liver tests should be obtained before starting BYLVAY and periodically during BYLVAY therapy. Inform patients or their caregiver(s) of the potential risk of hepatotoxicity, and that they will need to undergo monitoring for liver injury. Instruct patients or their caregiver(s) to immediately report any signs or symptoms of severe liver injury to their healthcare provider *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].*

Diarrhea

Advise patients or their caregiver(s) to notify their healthcare provider if they experience new onset or worsening of diarrhea *[see Warnings and Precautions (5.2)].*

Fat Soluble Vitamin (FSV) Deficiency

Advise patients or their caregiver(s) that INR (for vitamin K) and serum levels of vitamins A, D, E will be obtained before starting and periodically during treatment to assess for FSV deficiency *[see Warnings and Precautions (5.3)].* Inform patients or their caregiver(s) that they may bleed more easily or may bleed longer. Advise patients or their caregiver(s) to call their healthcare provider for any signs or symptoms of bleeding.

Pregnancy

Advise patients or their caregiver(s) that there is a pregnancy safety study that collects pregnancy outcome data in women taking BYLVAY during pregnancy. Pregnant women exposed to BYLVAY, or their healthcare providers, should report BYLVAY exposure by calling 1-855-463-5127 *[see Use in Specific Populations (8.1)]*.

Manufactured for:

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