PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrBYLVAY™

Odevixibat Capsules

Capsule; 200 mcg, 400 mcg, 600 mcg and 1200 mcg, Oral

Bile and Liver Therapy

Medison Pharma Canada Inc.
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Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

Contents

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BYLVAY (odevixibat) is indicated for:

- the treatment of pruritus in patients aged 6 months or older with progressive familial intrahepatic cholestasis (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.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of BYLVAY in pediatric patients aged 6 months or older has been established. Therefore, Health Canada has authorized an indication for pediatric use. The safety and efficacy of BYLVAY in pediatric patients < 6 months of age have not been established.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

Odevixibat is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- All available capsule strengths may be swallowed whole or opened and sprinkled. The strength chosen to support total daily dose should be based on predicted ease of administration for each patient, i.e., total number of capsules, size of capsules, ability to swallow whole capsules.
- For patients taking bile acid binding resins, take BYLVAY at least 4 hours before or 4 hours after taking a bile acid binding resin.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dose of BYLVAY is 40 mcg/kg administered orally once daily in the morning with a meal.

Dosage Adjustment

Improvement in pruritus and reduction of serum bile acid levels may occur gradually in some patients after initiating BYLVAY therapy. If an adequate clinical response has not been achieved after 3 months

of continuous therapy, the dose may be increased to 120 mcg/kg/day, with a maximum daily dose of 7200 mcg per day.

Table 1 below shows the recommended weight-based total daily dosage needed for the recommended dosage at 40 mcg/kg and 120 mcg/kg once daily.

Table 1 Recommended Dosage

Body weight (kg)	Total daily dosage (mcg) (for nominal dose of 40 mcg/kg/day)	Total daily dosage (mcg) (for nominal dose of 120 mcg/kg/day)
4 to 7.4	200	600
7.5 to 12.4	400	1200
12.5 to 17.4	600	1800
17.5 to 25.4	800	2400
25.5 to 35.4	1200	3600
35.5 to 45.4	1600	4800
45.5 to 55.4	2000	6000
55.5 and above	2400	7200

Special Populations

Renal Impairment: No dose adjustment is required for patients with mild or moderate renal impairment. There are no available clinical data for the use of BYLVAY in patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring haemodialysis (see 10.3 Pharmacokinetics).

Hepatic Impairment: No dose adjustment is required for patients with mild or moderate hepatic impairment (see 10.3 Pharmacokinetics).

No data are available for PFIC patients with severe hepatic impairment (Child Pugh C). Limited data are available in PFIC patients with cirrhosis or portal hypertension. Consider discontinuing BYLVAY if a patient progresses to portal hypertension, cirrhosis, or demonstrated hepatic decompensation. (see 7 WARNINGS AND PRECAUTIONS).

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

Pediatrics (<18 years of age): The safety and efficacy of BYLVAY in pediatric patients less than 6 months of age have not been established.

4.4 Administration

BYLVAY is for oral use. Administer BYLVAY in the morning with a meal.

The larger 200 mcg and 600 mcg capsules (Size 0) are intended to be opened and sprinkled on soft food or in a liquid but may be swallowed whole.

The smaller 400 mcg and 1200 mcg capsules (Size 3) are intended to be swallowed whole but may be

opened and sprinkled on soft food or in a liquid.

Administering the drug in a liquid requires the use of an oral syringe. Do not administer via a bottle or "sippy cup" because the pellets will not pass through the opening.

Pellets will not dissolve in liquids.

For capsules to be opened and sprinkled on soft food, the patient should be instructed to:

1. Place a small quantity (up to 30 mL/2 tablespoons) of soft food (yoghurt, apple sauce, oatmeal porridge, banana puree, carrot puree, chocolate-flavoured pudding or rice pudding) in a bowl. The food should be at or below room temperature.
2. Hold the capsule horizontally at both ends, twist in opposite directions and pull apart to empty the pellets into the bowl of soft food. The capsule should be gently tapped to ensure that all pellets will come out.
3. Repeat Step 2 if the dose requires more than one capsule.
4. Gently mix the pellets with a spoon into the soft food.
5. Administer the entire dose immediately after mixing. Do not store the mixture for future use.
6. Drink a glass of water or age-appropriate liquid following the dose.
7. Dispose all empty capsule shells.

For capsules to be opened and sprinkled in a liquid (requires use of an oral dose syringe 5mL or larger), the patient should be instructed to:

1. Hold the capsule horizontally at both ends, twist in opposite directions and pull apart to empty the pellets into a small mixing cup. The capsule should be gently tapped to ensure that all pellets will come out.
2. Repeat Step 1 if the dose requires more than one capsule.
3. Add 1 teaspoon (5 mL) of an age-appropriate liquid (for example, breast milk, infant formula, or water).
4. Let the pellets sit in the liquid for approximately 5 minutes to allow complete wetting. REMINDER: The pellets will not dissolve in the liquid.
5. 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.
6. Withdraw the entire contents into the oral syringe by pulling the plunger on the end of the syringe.
7. 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 the 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.
8. If any pellet/liquid mixture remains in the mixing cup, repeat Step 6 and Step 7 until the entire dose has been administered. Do not store the mixture for future use.
9. Follow the dose with water or an age-appropriate liquid (breast milk, infant formula).
10. Dispose of all empty capsule shells.

4.5 Missed Dose

If a dose of BYLVAY is missed, the patient should take the forgotten dose as soon as possible without exceeding one dose per day.

5 OVERDOSAGE

Symptoms
An overdose may result in symptoms resulting from an exaggeration of the known pharmacodynamic effects of the medicinal product, mainly gastrointestinal effects such as diarrhoea and vomiting.

Management
In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule, 200 mcg, 400 mcg, 600 mcg, 1200 mcg	Black iron oxide, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide (400 mcg and 1200 mcg capsules only), shellac, titanium dioxide, yellow iron oxide

BYLVAY is supplied in high-density polyethylene (HDPE) bottle with a tamper evident, child resistant polypropylene closure. Pack size of 30 capsules.

BYLVAY 200 mcg capsules
Size 0 capsule (21.7 mm × 7.64 mm) with ivory opaque cap and white opaque body; imprinted “A200” with black ink.

BYLVAY 400 mcg capsules
Size 3 capsule (15.9 mm × 5.82 mm) with orange opaque cap and white opaque body; imprinted “A400” with black ink.

BYLVAY 600 mcg capsules
Size 0 capsule (21.7 mm × 7.64 mm) with ivory opaque cap and body; imprinted “A600” with black ink.

BYLVAY 1200 mcg capsules
Size 3 capsule (15.9 mm × 5.82 mm) with orange opaque cap and body; imprinted “A1200” with black ink.

7 WARNINGS AND PRECAUTIONS

General

Odevixibat Response
The mechanism of action of odevixibat requires that the enterohepatic circulation of bile acids and bile salt transport into biliary canaliculi is preserved. Conditions, medications or surgical procedures that impair either gastrointestinal motility, or enterohepatic circulation of bile acids, including bile salt transport to biliary canaliculi have the potential to reduce the efficacy of odevixibat. For this reason, patients with pathologic variations (for example, of the ABCB11 gene) that predict complete absence of the BSEP protein or non-functional BSEP protein may not respond to odevixibat.

There are limited or no clinical data with odevixibat in PFIC subtypes other than 1 and 2.

Lipophilic medicinal products
The absorption of lipophilic medicinal products may be affected by concomitant use of BYLVAY. (see 9 DRUG INTERACTIONS).

Gastrointestinal

Diarrhoea
Diarrhoea has been reported as a common adverse reaction when taking BYLVAY. Diarrhoea may lead to dehydration. Patients should be monitored regularly to ensure adequate hydration during episodes of diarrhoea. Interruption of treatment should be considered during acute episodes of diarrhea and/or vomiting that risk dehydration.

Hepatic/Biliary/Pancreatic

Liver test abnormalities
In clinical trials, increased levels of liver enzymes and bilirubin were observed in some patients receiving BYLVAY. Assessment of hepatic laboratory tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase and total bilirubin) is recommended for all patients prior to initiating BYLVAY, with monitoring per standard clinical practice.

Limited data are available in PFIC patients with cirrhosis or portal hypertension. Consider discontinuing BYLVAY if a patient progresses to portal hypertension, cirrhosis or demonstrated hepatic decompensation.

Monitoring and Laboratory Tests

Fat-soluble vitamin deficiency
In clinical trials, decreased levels of fat-soluble vitamins A, D, E, and K (measured using international normalized ratio (INR)) and calcium were observed in some patients receiving BYLVAY. All observed decreases in calcium were not considered to be clinically significant by the investigators.

Assessment of fat-soluble vitamin levels (Vitamins A, D, E), calcium, and INR are recommended for all patients prior to initiating BYLVAY, with monitoring per standard clinical practice. Consider BYLVAY discontinuation for fat-soluble-vitamin deficiency refractory to supplementation.

Reproductive Health: Female and Male Potential

Women of childbearing potential should use an effective method of contraception when treated with BYLVAY. (see 9 DRUG INTERACTIONS).

- **Fertility**

  No fertility data are available in humans. Animal studies do not indicate any direct or indirect effects on fertility or reproduction.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of odevixibat in pregnant women. Animal studies have shown reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY). BYLVAY is not recommended during pregnancy and in women of childbearing potential not using contraception.

Women of childbearing potential should use an effective method of contraception when treated with BYLVAY (see 9 DRUG INTERACTIONS).

7.1.2 Breast-feeding

There are no data on the presence of odevixibat in human milk, the effects on the breastfed infant, or the effects on milk production.

A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from BYLVAY therapy, taking into account the benefit of breast-feeding for the child, the benefit of therapy for the mother, and any potential adverse effects on the breastfed child from odevixibat.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of BYLVAY in pediatric patients aged 6 months or older has been established. Therefore, Health Canada has authorized an indication for pediatric use. The safety and efficacy of BYLVAY in pediatric patients < 6 months of age have not been established.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of BYLVAY was evaluated in a total of 117 patients with PFIC treated with BYLVAY in two phase 3 clinical trials, including study A4250-005 (PEDFIC1), a randomized, double-blind, placebo-

controlled, 24-week study of two dose levels of BYLVAY (40 mcg/kg and 120 mcg/kg; n=61) administered once daily and study A4250-008 (PEDFIC2), an open-label 72-week study of BYLVAY 120 mcg/kg/day for continued treatment of patients in Study A4250-005 and enrollment of an additional cohort of patients with PFIC (n=56).

The very commonly reported adverse drug reactions (in ≥10%) in A4250-005 (PEDFIC1) were diarrhea (31%) and vomiting (17%). 8 patients experienced a treatment emergent serious adverse event in Study A4250-005.

In Study A4250-005, 1 patient in the 120 mcg/kg/day group discontinued study drug due to an adverse event (which was diarrhea). No patients in the 40 mcg/kg/day or placebo group experienced a TEAE leading to study drug discontinuation during Study A4250-005.

8.2 Clinical Trial Adverse Reactions

There is limited data on the safety of odevixibat in adults ≥ 18 years of age. The 5 patients ≥ 18 years of age were included in the long-term extension study A4250-008. The oldest patient was 26 years of age.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The most common adverse drug reactions were gastrointestinal and liver-chemistry abnormalities.

Table 3 Common Adverse Drug Reactions* in ≥ 2% of Patients in A4250-005 (PEDFIC1)

	Study A4250-005 (By Treatment)			
	Placebo (N=20) N (%)	**40 mcg/kg/day (N=23) N (%)**	**120mcg/kg/day (N=19) N (%)**	**Total BYLVAY 40 mcg/kg/day and 120mcg/kg/day (N=42) N (%)**
Blood and Lymphatic System Disorders				
Splenomegaly	0	0	2 (10.5)	2 (4.8)
Gastrointestinal Disorders				
Diarrhoea	1 (5.0)	9 (39.1)	4 (21.1)	13 (31.0)
Vomiting	0	4 (17.4)	3 (15.8)	7 (16.7)
Abdominal pain [a]	0	3 (13.0)	3 (15.8)	6 (14.3)
Gastro-oesophageal reflux disease	0	1 (4.3)	0	1 (2.4)
Mouth ulceration	0	0	1 (5.3)	1 (2.4)
Hepatobiliary disorders				
Cholelithiasis	0	0	1 (5.3)	1 (2.4)
Jaundice	0	1 (4.3)	0	1 (2.4)

	Study A4250-005 (By Treatment)			
	Placebo (N=20) N (%)	**40 mcg/kg/day (N=23) N (%)**	**120mcg/kg/day (N=19) N (%)**	**Total BYLVAY 40 mcg/kg/day and 120mcg/kg/day (N=42) N (%)**
Injury, Poisoning and Procedural Complications				
Lower limb fracture	0	1 (4.3)	0	1 (2.4)
Metabolism and Nutrition Disorders				
Dehydration	0	0	1 (5.3)	1 (2.4)
Skin and Subcutaneous Tissue Disorders				
Rash vesicular	0	1 (4.3)	0	1 (2.4)

a – Abdominal pain is a grouped term that includes abdominal discomfort, abdominal pain and abdominal pain upper
*Adverse Drug Reactions are based on as treatment emergent adverse events (TEAEs) being reported more frequently with odevixibat than with placebo, regardless of causality.

In the long-term follow-up Study A4250-008, adverse drug reactions were similar to those observed in Study A4250-005 (PEDFIC1). There was 1 recurrence of pancreatitis in the long-term follow up study (PEDFIC2).

Diarrheal adverse reactions
Treatment interruption was reported for diarrhoea in 4% of patients and discontinuation of BYLVAY due to diarrhoea was reported in 1%.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 4 Treatment-Emergent Adverse Events - Laboratory Abnormalities (≥2%) of Patients in the Pooled Population for Study A4250-005

	Study A4250-005 (By Treatment)			
	Placebo (N=20) N (%)	**40 mcg/kg/day (N=23) N (%)**	**120 mcg/kg/day (N=19) N (%)**	**Total BYLVAY 40 mcg/kg/day and 120 mcg/kg/day (n=42) N (%)**
Alanine aminotransferase increased	1 (5.0)	3 (13.0)	3 (15.8)	6 (14.3)
Blood bilirubin increased	2 (10.0)	3 (13.0)	2 (10.5)	5 (11.9)
Aspartate aminotransferase increased	1 (5.0)	2 (8.7)	1 (5.3)	3 (7.1)
Vitamin A deficiency	0	0	1 (5.3)	1 (2.4)
Vitamin E deficiency	0	0	1 (5.3)	1 (2.4)

ALT increased: Alanine Aminotransferase increased over baseline by ≥150 U/L
AST increased: Aspartate Aminotransferase increased over baseline by ≥150 U/L

In the long-term follow-up Study A4250-008, laboratory abnormalities were similar to those observed in Study A4250-005 (PEDFEC1).

In the randomized study A4250-005, 7% of odevixibat-treated patients and 0% of placebo-treated patients experienced calcium shifts to low.

In the long-term follow-up study A4250-008, 26% experienced calcium shifts to low. However, none of these laboratory abnormalities were reported as treatment-emergent adverse events.

All observed decreases in calcium were considered to be not clinically significant by the investigators.

8.5 Post-Market Adverse Reactions

Not Applicable.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in Table 5 are based on either drug interaction studies, or are potential interactions due to the expected magnitude and seriousness of the interaction.

Table 5 Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Bile acid binding resins e.g., cholestyramine, colesevelam, or colestipol	CT	Bile acid binding resins may bind odevixibat in the gut, reducing BYLVAY efficacy	Administer bile acid binding resins at least 4 hours before or 4 hours after administration of BYLVAY

Legend: CT = Clinical Trial

Interaction with lipophilic medicinal products
In an interaction study with a lipophilic combination oral contraceptive containing ethinyl estradiol (EE) (0.03 mg) and levonorgestrel (LVN) (0.15 mg) conducted in adult healthy females, concomitant use of BYLVAY 3 mg once daily for 6 days had no impact on the area under the curve (AUC) of LVN and decreased the AUC of EE by 17%, which is not considered clinically relevant.

Interaction studies with other lipophilic medicinal products have not been performed, therefore, an effect on the absorption of other fat-soluble medicinal products cannot be excluded.

Cytochrome P450-mediated interactions
In adult healthy subjects, concomitant use of BYLVAY 7.2 mg once daily for 4 days decreased the AUC of oral midazolam (a CYP3A4 substrate) by 30% and 1-OH-midazolam exposure by less than 20%, which is not considered clinically relevant.

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 at clinically relevant concentrations.

Transporter-mediated interactions
Odevixibat is a substrate of P-glycoprotein (P-gp) but not a substrate of breast cancer resistance protein (BCRP). In adult healthy subjects, coadministration of the strong P-gp inhibitor itraconazole increased the plasma exposure of a single dose of odevixibat 7.2 mg by approximately 50-60%, which is not expected to have a clinically significant effect.

In in vitro studies, odevixibat did not inhibit the transporters P glycoprotein (P-gp); breast cancer resistance protein (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).

9.5 Drug-Food Interactions

Administration of BYLVAY following a high-fat, high-calorie meal decreased the rate and extent of absorption and prolonged the time to reach maximum concentrations, relative to fasted conditions. Administration of BYLVAY, opened and sprinkled on applesauce, resulted in decreases in the rate and extent of absorption and prolonged the time to reach maximum concentrations compared to whole capsules administered under fasted conditions (see 10.3 PHARMACOKINETICS). The effect of food on the pharmacokinetics of odevixibat is not clinically significant. BYLVAY should be administered in the morning with a meal (see 4.4 Administration).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Odevixibat is a reversible, selective inhibitor of the ileal bile acid transporter (IBAT). It acts locally in the distal ileum to decrease the reuptake (of bile acids) from the terminal ileum and increase the clearance of bile acids through the colon, reducing the concentration of bile acids in the serum.

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.

10.2 Pharmacodynamics

Odevixibat reduces serum bile acids in patients with PFIC. In Study A4250-005, 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 14 CLINICAL TRIALS). 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.

10.3 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 (Cmax) could not be calculated.

Following a single administration of odevixibat 7.2 mg in healthy adults, the mean (%CV) Cmax and AUC0-24h 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. Peak odevixibat plasma concentration (C_{max}) is reached within 1 to 5 hours following a single administration of odevixibat 7.2 mg in healthy adults.

Effect of Food
Following administration of a single 9.6 mg dose of BYLVAY under high-fat, high-calorie fed conditions to healthy adult volunteers, a prolonged median Tmax from 3 hours to 4.5 hours and decreases of approximately 72% and 62% in Cmax and AUCT, respectively, were observed when compared to administration under fasted conditions.

Alternate Modes of Administration
Administration of a single 9.6 mg dose of BYLVAY sprinkled on applesauce resulted in a prolonged median Tmax (3 hours vs. 4.5 hours) and decreases of approximately 39% and 36% in Cmax and AUCT, respectively, compared to administration of intact capsules under fasted conditions.

The effect of food on the systemic exposure to odevixibat is not clinically significant. BYLVAY should be administered in the morning with a meal (see 4.4 Administration).

Distribution

Odevixibat is more than 99% bound to human plasma proteins.

Metabolism

Odevixibat is minimally metabolised in humans.

Elimination

Following administration of a single oral dose of 3 000 mcg of radiolabeled odevixibat in healthy adults,

the average percent recovery of the administered dose was 82.9% in faeces; less than 0.002% was recovered in the urine. More than 97% of faecal radioactivity was determined to be unchanged odevixibat.

The mean half-life was 2.36 hours in healthy adults following a single oral dose of 7.2 mg odevixibat.

Special Populations and Conditions

- **Hepatic Insufficiency** The majority of patients with PFIC presented with some degree of hepatic impairment because of the disease. Hepatic metabolism of odevixibat is not a major component of the elimination of odevixibat.
- **Renal Insufficiency** There are no available clinical data for the use of odevixibat in patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring haemodialysis. The impact of renal impairment on the pharmacokinetics of odevixibat is expected to be small due to low systemic exposure and the fact that odevixibat is minimally excreted in urine.

11 STORAGE, STABILITY AND DISPOSAL

Store in the original container at 15°C to 30°C. Protect from exposure to light.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

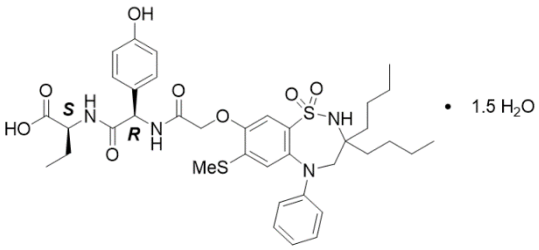
Drug Substance

Proper/Common name: odevixibat sesquihydrate

Chemical name: (2S)-2-{[(2R)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1λ6,2,5-benzothiadiazepin-8yl]oxy}acetamido)-2-(4 hydroxyphenyl)acetly]amino}butanoic acid sesquihydrate

Molecular formula and molecular mass: C37H48N4O8S2 x 1.5 H2O / 768.0 g/mol (anhydrous form / 740.9 g/mol)

Structural formula:



Physicochemical properties: Odevixibat sesquihydrate is a white to off-white solid. Its solubility in aqueous solutions is pH dependent and increases with increased pH.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

PFIC

Table 7 Summary of patient demographics for clinical trials in PFIC

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
A4250-005	Randomised (1:1:1), double-blind, placebo-controlled	40 mcg/kg/day, 120 mcg/kg/day odevixibat, oral Placebo 24-weeks	62 Total Subjects *17 (27%) PFIC1* *45 (73%) PFIC2* *42 odevixibat* *20 placebo*	3.2 years (0.5 to 15.9 years)	50% M

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
A4250-008[a]	Open-label extension	120 mcg/kg/day odevixibat, oral 72-weeks	112 Total subjects 35 (31%) PFIC 1 66 (59%) PFIC 2 7 (6%) PFIC3 2 (2%) PFIC4 2 (2%) PFIC6	5.3 years (0.5 to 19.5 years)	51% M

[a] data cut 7/31/2022

The efficacy of BYLVAY in patients with PFIC was evaluated in study A4250-005: a 24-week, randomised, double-blind, placebo-controlled trial conducted in 62 paediatric patients with a confirmed diagnosis of PFIC Type 1 or Type 2, who were aged 6 months to 17 years: each with serum bile acids ≥ 100 µmol/L and a history of significant pruritus (including a mean scratch score ≥ 2). Patients were randomised 1:1:1 to placebo, or 40 or 120 mcg/kg/day odevixibat and stratified by PFIC Type (1 or 2) and age (6 months to 5 years, 6 to 12 years, and 13 to ≤ 18 years). Reasons for patient exclusion included pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein, liver transplant, history of other liver disease, hepatic decompensation, abnormal intestinal motility or malabsorption, active infection, INR > 1.4, ALT > 10 × ULN or bilirubin > 10 × ULN. 13% of the patients had prior biliary diversion surgery. Patients completing study A4250-005 were eligible to enrol in study A4250-008, a 72-week open-label extension trial.

The primary endpoint in study A4250-005 was the proportion of patients with at least a 70% reduction in fasting serum bile acid levels or who achieved a level ≤ 70 µmol/L at Week 24. The proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on an observer-reported outcome (ObsRO) instrument was a secondary endpoint. Given the patients' young age, 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). A positive pruritus assessment was a score of ≤ 1 or at least 1-point improvement from baseline.

Median (range) age of patients in Trial 1 was 3.2 (0.5 to 15.9) years; 3 patients were older than 12 years of age. None were more than 18 years of age. 50% were male and 84% were white. At baseline, 81% of patients were treated with UDCA, 66% with rifampicin, and 89% with UDCA and/or rifampicin.

Baseline hepatic impairment per Child-Pugh classification was mild in 66%, moderate in 34%, and severe in 0% of patients. Baseline mean (SD) eGFR was 164 (30.6) mL/min/1.73 m^2. Baseline mean (SD) ALT, AST and bilirubin levels were 99 (116.8) U/L, 101 (69.8) U/L, and 3.2 (3.57) mg/dL, respectively. Baseline mean (SD) pruritus score (range: 0-4) and serum bile acids levels were similar in BYLVAY-treated patients (2.9 [0.089] and 252.1 [103.0] µmol/L, respectively) and placebo-treated patients (3.0 [0.143] and 247.5 [101.1] µmol/L, respectively).

14.2 Study Results

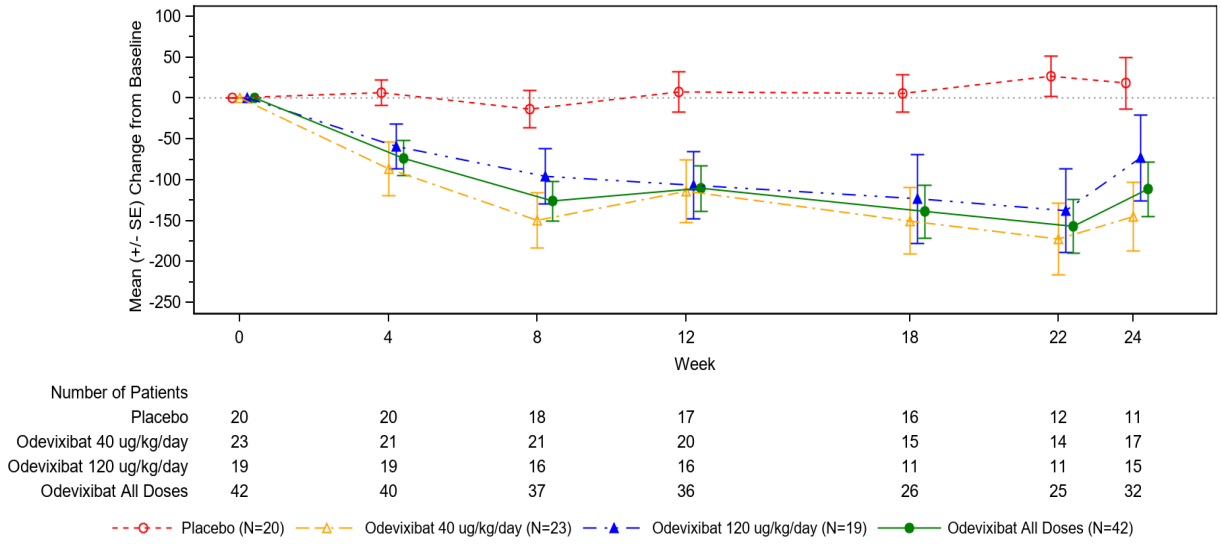
Table 8 presents the results of the comparison of the key efficacy results in study A4250-005 between BYLVAY and placebo. These data are displayed graphically over the 24-week treatment period in Figure 1 (serum bile acids) andFigure 2 (scratching scores).

Table 8 - Results of study A4250-005

Primary and Secondary Endpoints	Placebo (N=20)	BYLVAY		
		40 mcg/kg/day (N=23)	BYLVAY 120 mcg/kg/day (N=19)	Total (N=42)
Proportion of patients with significant reduction in serum bile acids at end of treatment[c]				
n (%) (95% CI)	0 (0.00, 16.84)	10 (43.5) (23.19, 65.51)	4 (21.1) (6.05, 45.57)	14 (33.3) (19.57, 49.55)
Difference in proportion vs. placebo (95% CI)		0.44 (0.22, 0.66)	0.21 (0.02, 0.46)	0.31 (0.09, 0.50)
One-sided p-value[a]		0.0015	0.0174	0.0015
Proportion of positive pruritus assessments over the treatment period				
Mean	28.74	58.31	47.69	53.51
LS Mean Difference (SE) vs placebo (95% CI)[b]		28.23 (9.18) (9.83, 46.64)	21.71 (9.89) (1.87, 41.5)	24.97 (8.24) (8.45, 41.49)

[a]Based on Cochran Mantel Haenszel test stratified by PFIC Type. P-values for the dose groups are adjusted for multiplicity.
[b]Based on an analysis of covariance model with daytime and nighttime baseline pruritus scores as covariates and treatment group and stratification factors (PFIC Type and age category) as fixed effects. LS: Least squares.
[c]at least a 70% reduction in fasting serum bile acid levels from baseline or who achieved a level ≤ 70 µmol/L at Week 24

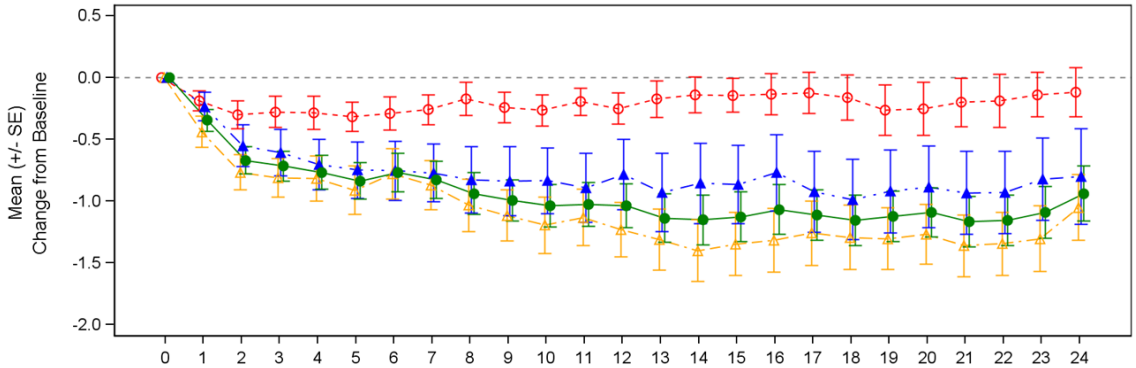
Figure 1 Mean (±SE) change from baseline in serum bile acid concentration (µmol/L) over time



Number of Patients							
Placebo	20	20	18	17	16	12	11
Odevixibat 40 ug/kg/day	23	21	21	20	15	14	17
Odevixibat 120 ug/kg/day	19	19	16	16	11	11	15
Odevixibat All Doses	42	40	37	36	26	25	32

Placebo (N=20) Odevixibat 40 ug/kg/day (N=23) Odevixibat 120 ug/kg/day (N=19) Odevixibat All Doses (N=42)

Figure 2 Mean (±SE) change from baseline in pruritus (scratching) severity score over time



Number of Patients																									
Placebo	20	20	20	20	20	20	20	20	20	20	20	20	20	18	18	17	17	17	16	15	15	15	15	13	12
Odevixibat 40 ug/kg/day	23	23	23	23	23	23	23	22	22	23	23	23	23	19	19	19	19	20	19	18	19	19	19	19	17
Odevixibat 120 ug/kg/day	19	19	19	19	19	19	19	19	19	18	18	18	18	16	16	16	16	16	16	16	16	16	16	15	14
Odevixibat All Doses	42	42	42	42	42	42	42	41	41	41	41	41	41	35	35	35	35	36	35	34	35	35	35	34	31

Placebo (N=20) Odevixibat 40 ug/kg/day (N=23) Odevixibat 120 ug/kg/day (N=19) Odevixibat All Doses (N=42)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: During single-dose studies 2000 mg/kg was the highest dosage tested in mice and rats with no pathologic findings. The major clinical signs in mice were diarrhoea and transient body-weight loss. Rats were asymptomatic.

In the repeat-dose studies involving mice, rats, dogs, and marmosets, no drug-related deaths were reported, except for male mice treated orally with 300 mg/kg/day during a 13-week study. These mice

showed clinical deterioration before euthanasia, characterized by decreased activity, cold body surface, piloerection, and slow/labored breathing. However, no specific microscopic cause of death could be identified. These deaths were attributed to drug administration and occurred at a systemic exposure level 490 times higher than the human equivalent.

The NOAEL (no observed adverse effect level) in the 26-week oral toxicity study in rats and the 39-week oral toxicity study in dogs was 300 mg/kg/day and 150 mg/kg/day, respectively, approximately 732 and 31 times the maximum recommended dose, respectively.

Carcinogenicity: 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 491 times the maximum recommended dose, respectively.

Genotoxicity: Odevixibat was negative in both Salmonella typhimurium LT2 and Escherichia coli WP2 strains, the mouse lymphoma cell forward mutation assay, and in vivo, rat micronucleus.

Reproductive and Developmental Toxicology: In pregnant New Zealand White rabbits, early delivery/abortion was observed in two rabbits receiving odevixibat during the period of foetal organogenesis at an exposure multiple of ≥ 2.3 of the anticipated clinical exposure (based on total plasma odevixibat AUC_{0-24}). Reductions in maternal body weight and food consumption were noted in all dose groups (transient at the exposure multiple 1.1 of the anticipated dose).

Starting from the exposure multiple of 1.1 of the clinical human exposure (based on total plasma odevixibat AUC_{0-24}), 7 foetuses (1.3% of all foetuses from odevixibat exposed does) in all dose groups were found to have cardiovascular defects (i.e. 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). No such malformations were observed when odevixibat was administered to pregnant rats. Because of the findings in rabbits, an effect of odevixibat on cardiovascular development cannot be excluded.

Odevixibat had no effect on the reproductive performance, fertility, embryo-foetal development, or prenatal/postnatal development studies in rats at the exposure multiple of 133 of the anticipated clinical exposure (based on total plasma odevixibat AUC_{0-24}), including juveniles (exposure multiple of 63 of the anticipated human exposure).

There is insufficient information on the excretion of odevixibat in animal milk. The presence of odevixibat in breast milk was not measured in animal studies. Exposure was demonstrated in the pups of lactating dams in the pre- and post-natal developmental toxicity study with rats (3.2-52.1% of the odevixibat plasma concentration of the lactating dams). It is therefore possible that odevixibat is present in breast milk.

In pregnant rats, given radioactive 2.5 µmol/kg odevixibat intravenously at day 18 of gestation, the radioactivity was rapidly distributed throughout the body of the dam (including the placenta and amnion membrane). Radioactivity passed the placenta and was detectable in low concentrations at 4 hours post-injection in the fetal liver only. In the fetuses, the radioactivity was below the limit of detection at 24 hour post administration.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrBYLVAY™

Odevixibat capsules

Read this carefully before you start taking **BYLVAY** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BYLVAY**.

What is BYLVAY used for?

BYLVAY is used to treat itch in progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older. PFIC is a liver disease caused by build-up of bile acids (cholestasis) that gets worse over time and is often accompanied with severe itching.

How does BYLVAY work?

BYLVAY contains the active substance odevixibat. Odevixibat is a medicine which increases the removal of substances called bile acids from the body. Bile acids are components of the digestive fluid called bile. It is produced by the liver and secreted into the intestines. Odevixibat blocks the mechanism that normally reabsorbs them from the intestines after they have done their job. This allows them to pass out of the body in the stool.

What are the ingredients in BYLVAY?

Medicinal ingredients: odevixibat sesquihydrate

Non-medicinal ingredients: Black iron oxide, hypromellose, microcrystalline cellulose, propylene glycol, red iron oxide (400 mcg and 1200 mcg capsules only), shellac, titanium dioxide, yellow iron oxide

BYLVAY comes in the following dosage forms:

Capsules, 200 mcg, 400 mcg, 600 mcg and 1200 mcg

Do not use BYLVAY if:

- You are allergic to any ingredients in this drug.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BYLVAY. Talk about any health conditions or problems you may have, including if you:

- been diagnosed with a complete absence or lack of function of bile salt export pump protein
- severely reduced liver function
- reduced stomach or bowel motility (movement of food throughout the body), or reduced circulation of bile acids between liver, bile and small intestine due to medicines, and/or surgical procedures.

Other warnings you should know about:

Talk to your doctor if you develop diarrhoea while taking BYLVAY. If you have diarrhoea, drink enough liquid to prevent dehydration.

Your doctor may recommend more frequent monitoring if you have abnormal liver function test results.

Your doctor may recommend assessment of Vitamin A, D and E blood levels and the blood clotting value called INR prior to and during BYLVAY treatment.

Children

Bylvay is not recommended for babies under 6 months because it is not known if the medicine is safe and effective in this age group.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

BYLVAY is not recommended during pregnancy and in women who can get pregnant but are not using contraception.

It is not known if BYLVAY can pass into breast milk and affect the baby. Your doctor will help you to decide whether to stop breast-feeding or avoid BYLVAY treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with BYLVAY:

- Treatment with BYLVAY may affect the absorption of fat-soluble vitamins such as Vitamin A, D and E, calcium, and fat-soluble medicines.

How to take BYLVAY:

- Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
- The dose of BYLVAY is based on your weight. Your doctor will work out the right number and strength of capsules for you to take.

Usual dose:

40 micrograms BYLVAY per kilogram body weight once daily

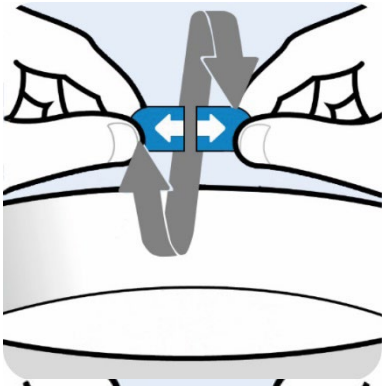
If the medicine is not working well enough after 3 months, your doctor may increase the dose to 120 micrograms BYLVAY per kilogram body weight (up to a maximum of 7200 micrograms once daily).

Take the capsules once daily in the morning with a meal.

All capsules can be either swallowed whole with a glass of water or opened and sprinkled on soft food or in a liquid.

Instructions to open capsules and sprinkle the contents on soft food:

Step 1: Place a small amount of soft food into a bowl (2 tablespoons/30 mL of yoghurt, apple sauce, banana or carrot puree, chocolate pudding, rice pudding or oatmeal porridge). Food should be at or below room temperature.



Step 2: Hold the capsule horizontally at both ends, twist in opposite directions.

Step 3: Pull apart to empty the contents into the bowl of soft food.

Step 4: Gently tap the capsule to ensure that all pellets come out.

Step 5: Repeat Steps 2, 3, and 4 if the dose requires more than one capsule.

Step 6: Gently mix the contents of the capsule into the soft food. Note that the pellets will not dissolve.

Step 7: Take the entire dose mixed into the soft food right away. Do not store the mixture for future use.

Step 8: Drink water or give an age-appropriate liquid, such as breast milk or infant formula, after the dose is taken to make sure any remaining soft food and pellet mixture is swallowed.

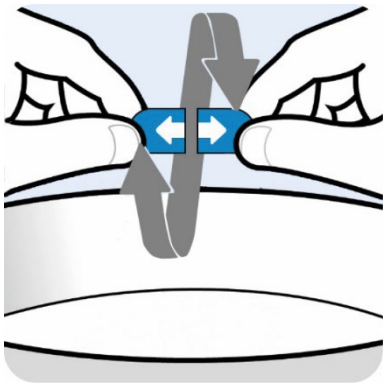
Step 9: Throw away all empty capsule shells in the trash.

Instructions to open capsules and sprinkle the contents in liquids:

If you are sprinkling the contents of the capsules in a liquid, you will need to use an oral syringe that holds 5mL or more.
Do not administer using a bottle or "sippy cup" because the liquid and pellet mixture will not pass through the opening. The pellets do not dissolve in liquids.

Step 1: Give BYLVAY with the first morning meal.

Step 2: Hold the capsule horizontally at both ends, twist in opposite directions.



Step 3. Pull apart and empty the contents into a small mixing cup.

Step 4: Gently tap the capsule shell to ensure that all pellets have been emptied into the mixing cup.

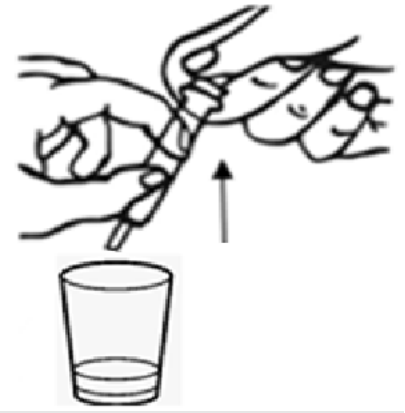
Step 5. If the dose requires more than 1 capsule, repeat Steps 2, 3, and 4.

Step 6. Add 1 teaspoon (5 mL) of an age-appropriate liquid (for example, breast milk, infant formula, or water).

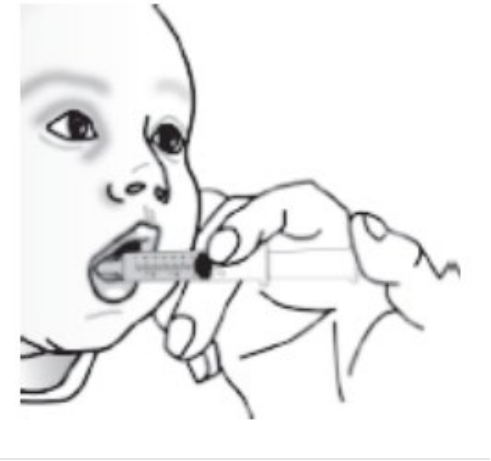
Step 7. Let the pellets sit in the liquid for about 5 minutes to allow complete wetting. REMINDER: The pellets will not dissolve in the liquid.

Step 8. 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 and pellet mixture into the syringe. Gently push the plunger down again to expel the liquid and pellet mixture back into the mixing cup. Do this 2 to 3 times to ensure complete mixing of the pellets into the liquid.

Step 9. Withdraw the entire contents of the mixing cup into the syringe by pulling the plunger on the end of the syringe.



Step 10. Place the tip of the syringe between the tongue and the side of the mouth, and then gently push the plunger down to squirt the liquid and pellet mixture between the tongue and the side of the mouth. Do not squirt the liquid and pellet mixture in the back of the throat because this could cause gagging or choking.



Step 11. Repeat Steps 9 and 10 until the entire dose (all of the liquid and pellet mixture in the cup) has been given. Do not store the mixture for future use.

Step 12. Drink water or give an age-appropriate liquid, such as breast milk or infant formula, to make sure any liquid and pellet mixture remaining in the mouth is swallowed.

Step 13. Dispose of (throw away) all empty capsule shells in the trash.

Overdose:

If you or the person you are caring for have taken too much BYLVAY, you may have side effects such as vomiting and diarrhea.

If you think you, or a person you are caring for, have taken too much BYLVAY, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Do not take a double dose to make up for a forgotten dose. Take the next dose at the usual time.

What are possible side effects from using BYLVAY?

These are not all the possible side effects you may have when taking BYLVAY. If you or your child experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- vomiting
- diarrhea
- abdominal (belly) pain

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store BYLVAY at room temperature (15°C to 30°C). Protect from exposure to light.
- Keep out of the reach and sight of children.

If you want more information about BYLVAY:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.medisonpharma.com, or by calling 1-800-696-1341

This leaflet was prepared by Medison Pharma Canada Inc.

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