1. NAME OF THE MEDICINAL PRODUCT

Bylvay® 200 micrograms hard capsules
Bylvay® 400 micrograms hard capsules
Bylvay® 600 micrograms hard capsules
Bylvay® 1200 micrograms hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bylvay® 200 micrograms hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 200 micrograms odevixibat.

Bylvay® 400 micrograms hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 400 micrograms odevixibat.

Bylvay® 600 micrograms hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 600 micrograms odevixibat.

Bylvay® 1200 micrograms hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 1200 micrograms odevixibat.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Bylvay® 200 mcg hard 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 hard 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 hard capsules

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

Bylvay® 1200 mcg hard capsules

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bylvay® is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months and older (see sections 4.4 and 5.1).

Bylvay® is indicated for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months and older (see sections 4.4 and 5.1).
The indication in ALGS is based on clinical trial data in children aged 12 months and above. Continued approval for use in patients below 12 months of age is contingent upon verification and description of clinical benefit in this age group based on clinical trial data.

4.2 Posology and method of administration

Treatment must be initiated and supervised by physicians experienced in the management of PFIC and ALGS.

Posology in PFIC
The recommended dose of odevixibat for the treatment of PFIC is 40 mcg/kg administered orally once daily in the morning.

Dose escalation
In patients with PFIC, improvement in pruritus and reduction of serum bile acid levels may occur gradually in some patients after initiating odevixibat therapy. If an adequate clinical response has not been achieved after 3 months continuous therapy, the dose may be increased to 120 mcg/kg/day, with a maximum daily dose of 7200 mcg (see section 4.4).

Posology in ALGS
The recommended dose of odevixibat for treatment of ALGS is 120 mcg/kg administered orally once daily in the morning.

Dose reduction
In patients with ALGS, dose reduction to 40 mcg/kg/day may be considered if tolerability issues occur in the absence of other causes. Once tolerability issues stabilise, increase to 120 mcg/kg/day.

All available capsule strengths are interchangeable and 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 (Table 1).

Table 1: Recommended dosage

Body weight (kg)	Total daily dose (mcg) (for nominal dose of 40 mcg/kg/day)	Total daily dose (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

Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with odevixibat.

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

Special populations

Renal impairment
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 (see section 5.2). However, due to the minimal plasma concentrations and negligible renal excretion, no dose adjustment is required for patients with renal impairment.

Hepatic impairment
No dose adjustment is required for patients with mild or moderate hepatic impairment (see sections 5.1 and 5.2). Odevixibat has not been sufficiently studied in patients with severe hepatic impairment (Child-Pugh C). Due to minimal absorption, no dose adjustment is required, however additional monitoring for adverse reactions may be warranted in these patients when odevixibat is administered (see section 4.4).

Elderly
The safety and effectiveness of Bylvay® in adult patients, including those 65 years of age and older, have not been established.

Paediatric population
The safety and efficacy of Bylvay® in PFIC patients less than 6 months of age have not been established.

The safety and efficacy of Bylvay® in ALGS patients less than 6 months of age have not been established.

Method of administration
Bylvay® is for oral use. To be taken with or without food in the morning (see section 5.2).

The larger 200 mcg and 600 mcg capsules 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 are intended to be swallowed whole but may be opened and sprinkled on soft food or in a liquid.
If the capsule is to be swallowed whole, the patient should be instructed to take it with a glass of water in the morning.

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 (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 following the dose.
7. Dispose of all empty capsule shells.

For capsules to be opened and sprinkled in a liquid (requires use of an oral dose syringe), 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.
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 patient's tongue and the side of the mouth. Do not squirt liquid/pellet in the back of the patient'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 breast milk, infant formula or other age-appropriate liquid.
10. Dispose of all empty capsule shells.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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, PFIC patients with pathologic variations of the ABCB11 gene that predict non-functional or complete absence of the Bile Salt Export Pump (BSEP) protein may not respond to odevixibat.

Liver monitoring
Elevations in liver enzymes and bilirubin levels have been noted in patients treated with odevixibat. Assessment of liver function tests is recommended for patients prior to initiating Bylvay®, with monitoring per standard of care. For patients with liver function test elevations and severe hepatic impairment (Child-Pugh C), more frequent monitoring is to be considered.

Diarrhoea
Diarrhoea has been reported as a common adverse reaction when taking odevixibat. Diarrhoea may lead to dehydration. Patients should be monitored regularly to ensure adequate hydration during episodes of diarrhoea (see section 4.8). Treatment interruption or discontinuation may be required for persistent diarrhoea.

Fat-soluble vitamin deficiency
Assessment of fat-soluble vitamin (FSV) levels (Vitamins A, D, E) and international normalised ratio (INR) are recommended for all patients prior to initiating Bylvay®, with monitoring per standard clinical practice. If FSV deficiency is diagnosed, supplemental therapy should be prescribed.

Lipophilic medicinal products
The absorption of lipophilic medicinal products may be affected by concomitant use of odevixibat (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Transporter-mediated interactions
Odevixibat is a substrate for the efflux transporter P-glycoprotein (P-gp). In adult healthy subjects, co-administration of the strong P-gp inhibitor itraconazole increased the plasma exposure of a single dose of odevixibat 7200 mcg by approximately 50-60%. This increase is not considered clinically relevant. No other potentially relevant transporter-mediated interactions were identified *in vitro* (see section 5.2).

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 odevixibat 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.

In clinical trials, decreased levels of fat-soluble vitamins were observed in some patients receiving odevixibat. Levels of fat-soluble vitamins should be monitored (see section 4.4).

Cytochrome P450-mediated interactions
In *in vitro* studies, odevixibat did not induce CYPs 1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 at clinically relevant concentrations, but was shown to be an inhibitor of CYP3A4/5 (see section 5.2).

In adult healthy subjects, concomitant use of odevixibat decreased the area under the curve (AUC) of oral midazolam (a CYP3A4 substrate) by 30% and 1-OH-midazolam exposure by less than 20%, which is not considered clinically relevant.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data from the use of odevixibat in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). 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 section 4.5).

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 (see section 5.3).

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 and the benefit of therapy for the mother.

Fertility
No fertility data are available in humans. Animal studies do not indicate any direct or indirect effects on fertility or reproduction (see section 5.3).

4.7 Effects on ability to drive and use machines

Bylvay® has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

PFIC
Summary of the safety profile
The most commonly reported adverse reaction was diarrhoea.

Other reported adverse reactions were vomiting and stomach pain, mild or moderate increases in liver function tests, and decreases in vitamin D and E levels.

Tabulated list of adverse reactions

Adverse reactions are ranked according to system organ class, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Table 2 lists adverse reactions identified in clinical trials in patients with PFIC aged between 4 months to 25 years of age (median 3 years 7 months).

Table 2: Frequency of adverse reactions reported in patients with PFIC

MedDRA system organ class	**Frequency**	**Adverse Reaction**
Gastrointestinal disorders	Very common	diarrhoea[a] vomiting abdominal pain[b]
Hepatobiliary disorders	Very common	blood bilirubin increased alanine aminotransferase increased
	Common	Hepatomegaly aspartate aminotransferase increased
Metabolism and nutrition site disorders	Very common	vitamin D deficiency
	Common	vitamin E deficiency

[a] Based on the combined frequency of diarrhoea, diarrhoea haemorrhagic and faeces soft

[b] Includes abdominal pain upper

Description of selected adverse reactions

Gastrointestinal disorders adverse reactions

In clinical trials, diarrhoea was not the most common gastrointestinal adverse drug reaction. Adverse reactions of diarrhoea, diarrhoea haemorrhagic and faeces soft were of short duration with most events ≤ 5 days in duration. Most cases of diarrhoea were mild to moderate in intensity and non-serious. Dose reduction, treatment interruption and discontinuation due to diarrhoea was reported with few patients requiring intravenous or oral hydration due to diarrhoea (see section 4.4).

Other commonly reported gastrointestinal disorders were vomiting and abdominal pain (including abdominal pain upper and lower), all nonserious, mild to moderate and in general not dose limiting.

Hepatobiliary disorders

The most common hepatic adverse reactions were increases in blood bilirubin, aspartate aminotransferase and alanine aminotransferase (AST and ALT). Majority of these were mild to moderate in severity. Treatment interruption due to increases in liver function tests have been seen in patients with PFIC treated with odevixibat. Most excursions in ALT, AST, and bilirubin values were also considered related to the underlying disease, as well as intermittent concomitant viral or infectious illnesses, which are common at the age of the patients, hence, monitoring of liver function tests is recommended (see section 4.4).

Metabolism and nutrition disorders

Due to decreased release of bile acids into the intestine and malabsorption, patients with PFIC are at risk for fat-soluble vitamin deficiency (see section 4.4). Reductions in vitamin levels were observed during long-term treatment with odevixibat; the majority of these patients responded to appropriate vitamin supplementation. Overall, few patients had fat-soluble vitamin deficiency that was refractory to supplementation. These events were mild in intensity and did not lead to discontinuation of odevixibat.

Post-marketing experience

The adverse reactions observed in post-marketing were consistent with those seen in clinical trials. Data are insufficient to provide an estimate of incidence in the PFIC population.

ALGS

Summary of the safety profile

The most commonly reported adverse reaction was diarrhoea. Other reported adverse reactions were vomiting and stomach pain, mild to moderate increases in liver function tests, and decreases in vitamin D and E levels.

Tabulated list of adverse reactions

Adverse reactions are ranked according to system organ class, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Table 3 lists adverse reactions identified in clinical trials in patients with ALGS aged between 6 months to 15.5 years of age (median 5 years 8 months).

Table 3: Frequency of adverse reactions reported in patients with ALGS

MedDRA system organ class	Frequency	Adverse Reaction
Gastrointestinal disorders	Very common	diarrhoea abdominal pain[a]
	Common	vomiting
Hepatobiliary disorders	Common	hepatomegaly alanine aminotransferase increased aspartate aminotransferase increased gamma-glutamyl transferase increased blood bilirubin increased
Metabolism and nutrition site disorders	Very common	vitamin D deficiency
	Common	vitamin E deficiency

[a] Includes abdominal pain upper

Description of selected adverse reactions

Gastrointestinal disorders adverse reactions

Most frequently reported adverse drug reaction was diarrhoea, mostly mild to moderate in severity and non-serious. Few patients required treatment interruption and rehydration due to diarrhoea (see section 4.4). Other gastrointestinal adverse reactions were reports of abdominal pain and vomiting, mild to moderate in severity and in most cases of limited duration.

Hepatobiliary disorders

The most common hepatic adverse reactions were increases in blood bilirubin, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase (ALT, AST and GGT). Most of these excursions were mild in severity and non-serious, and increases were not indicative of drug-induced liver injury. Elevations in liver enzymes and bilirubin levels were observed due to the underlying hepatic pathophysiology of ALGS, hence the monitoring of liver function tests is recommended (see section 4.4).

Metabolism and nutrition disorders

Due to the decreased release of bile acids into the intestine and risk of malabsorption, paediatric patients with ALGS with chronic cholestasis are at risk of fat-soluble vitamin deficiencies even with supplementation (see section 4.4). Reductions in vitamin levels were observed during long-term treatment with odevixibat; the majority of these patients responded to appropriate vitamin supplementation. Overall, few patients had fat-soluble vitamin deficiencies that were refractory to supplementation. These events were mild in intensity and did not lead to treatment interruption or discontinuation of odevixibat.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, other drugs for bile therapy
ATC code: A05AX05

Mechanism of action
Odevixibat is a reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT). It acts locally in the distal ileum to decrease the re-uptake of bile acids (primarily the salt forms) and increase the clearance of bile acids through the colon, reducing the concentration of bile acids in the serum.

Pharmacodynamic effects
Odevixibat acts locally in the distal ileum to decrease the reuptake of bile acids and increase the clearance of bile acids through the colon, reducing the concentration of bile acids in the serum. The extent of reduction of serum bile acids does not correlate with systemic PK.

Clinical efficacy and safety

Clinical trials in PFIC
The efficacy of Bylvay® in patients with PFIC was evaluated in two phase 3 trials. PFIC Trial 1 (Study A4250-005) was a 24-week, randomised, double-blind, placebo-controlled trial conducted in 62 patients with a confirmed diagnosis of PFIC Type 1 or Type 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). Patients with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein and those with ALT > 10 × ULN or bilirubin > 10 × ULN were excluded. 13% of the patients had prior biliary diversion surgery. Patients completing PFIC Trial 1 were eligible to enrol in PFIC Trial 2 (Study A4250-008), a 72-week open-label extension trial. In total, 116 patients were enrolled in Trial 2, including 37 patients who received odevixibat in Trial 1 and 79 patients who were treatment naïve. Results were analysed for Trial 1, and pooled for Trials 1 and 2, representing 96 weeks of treatment for patients that completed treatment with odevixibat in both trials.

The primary endpoint in PFIC Trial 1 and Trial 2 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. A positive pruritus assessment was a score of ≤ 1 or at least 1-point improvement from baseline. Pruritus assessments were conducted in the morning and evening using a 5-point scale (0-4). Additional secondary endpoints included changes from baseline to end of treatment in growth, sleep parameters (per ObsRO) and ALT.

Median (range) age of patients in Trial 1 was 3.2 (0.5 to 15.9) years; 50% were male and 84% were white. 27% of patients had PFIC Type 1 and 73% had PFIC Type 2. 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% and moderate in 34% of patients. Baseline mean (SD) eGFR was 164 (30.6) mL/min/1.73m^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 odevixibat-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). Demographic and baseline characteristics of the pooled phase 3 population were generally consistent with the Study A4250-005 population. 36 (30%) of patients had PFIC Type 1, 70 (58%) had PFIC Type 2; 7 (6%) had PFIC Type 3, 4 (3%) had the episodic form of PFIC, and 2 (2%) each had PFIC Type 4 and PFIC Type 6.

Table 4 presents the results of the comparison of the key efficacy results in PFIC Trial 1 between odevixibat and placebo. These data are displayed graphically over the 24-week treatment period in Figure 1 (serum bile acids) and Figure 2 (scratching scores).

Table 4: Comparison of key efficacy results for odevixibat vs. placebo over the 24-week treatment period (PFIC in Trial 1)

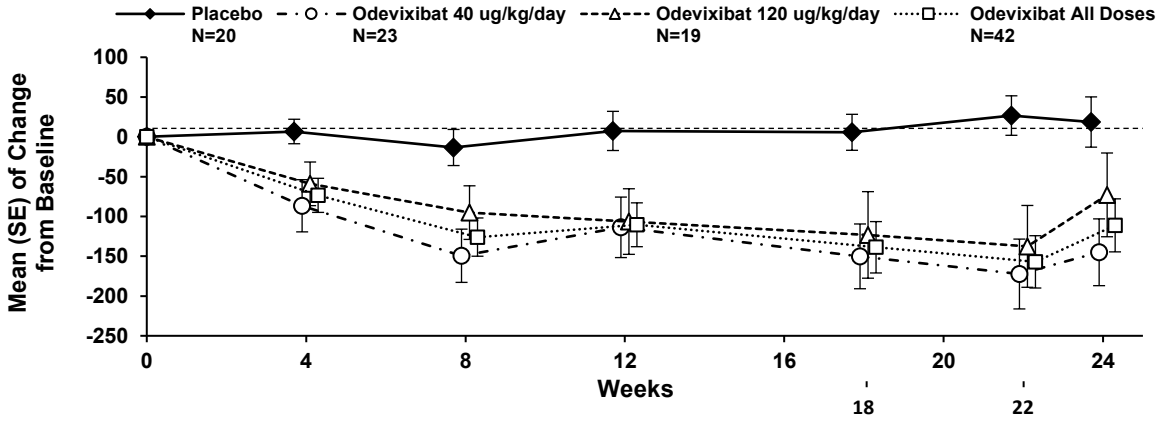
Efficacy endpoint	Placebo (N=20)	Odevixibat		
		40 mcg/kg/day (N=23)	120 mcg/kg/day (N=19)	Total (N=42)
Proportion of patients with reduction in serum bile acids at end of treatment (responders[a])				
n (%) (95% CI)	0 (0.00, 16.84)	10 (43.5) (23.19, 65.51)	4 (21.1) (6.05, 45.57)	14 (33.3) (19.57, 49.55)
Difference in proportion vs. placebo (95% CI)		0.44 (0.22, 0.66)	0.21 (0.02, 0.46)	0.33 (0.09, 0.50)
One-sided p-value[b]		0.0015	0.0174	0.0015
Proportion of positive pruritus assessments over the treatment period				
Proportion	28.74	58.31	47.69	53.51
Difference in proportion (SE) vs. placebo (95% CI)[c]		28.23 (9.18) (9.83, 46.64)	21.71 (9.89) (1.87, 41.54)	24.97 (8.24) (8.45, 41.49)

[a] Responders were defined as at least a 70% reduction in serum bile acids concentration from baseline or reaching a level ≤ 70 µmol/L.

[b] Based on Cochran Mantel Haenszel test stratified by PFIC Type. P-values for the dose groups are adjusted for multiplicity.

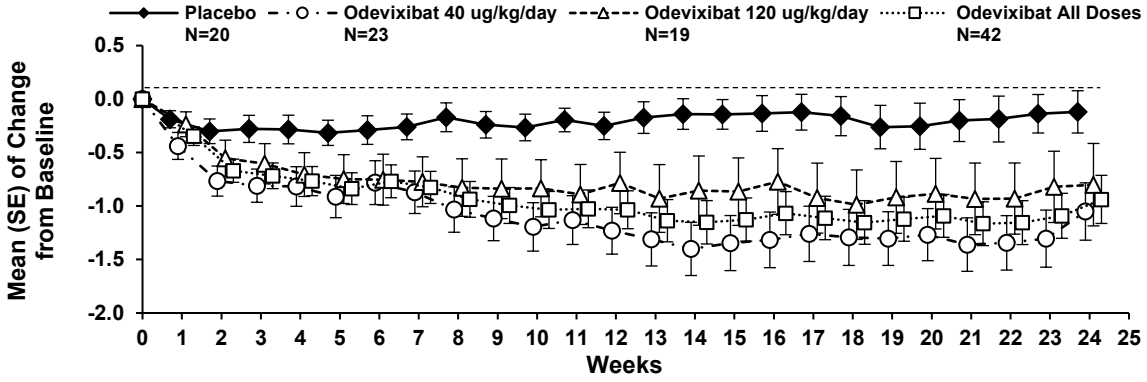
[c] Based on least squares means from an analysis of covariance model with daytime and night-time baseline pruritus scores as covariates and treatment group and stratification factors (PFIC Type and age category) as fixed effects.

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



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

Figure 2: Mean (±SE) change from baseline in pruritus (scratching) severity score over time (PFIC Trial 1)



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**
40 µg/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**
120 µg/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**
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**

In addition to the results for reduction of pruritus (scratching), odevixibat reduced the percentage of days the patient required soothing, and patients less often required help falling asleep and had fewer days needing to sleep with a caregiver. Treatment with odevixibat also led to improvements from baseline in liver function test results (Table 5). The effect of odevixibat on growth parameters over 24 weeks is also presented.

Table 5: Comparison of efficacy results for growth and hepatic biochemical parameters for odevixibat vs. placebo over the 24-week treatment period (PFIC Trial 1)

Efficacy endpoint	Placebo (N=20)	Odevixibat		
		40 mcg/kg/day (N=23)	120 mcg/kg/day (N=19)	Total (N=42)
Alanine aminotransferase (U/L) (mean [SE])				
Baseline	76.9 (12.57)	127.7 (34.57)	89.1 (19.95)	110.2 (20.96)
Change to Week 24	3.7 (4.95)	-27.9 (17.97)	-25.3 (22.47)	-26.7 (13.98)
Mean difference vs. placebo (95% CI)[a]		-14.8 (16.63) (-48.3, 18.7)	-14.9 (17.25) (-49.6, 19.9)	-14.8 (15.05) (-45.1, 15.4)
Aspartate aminotransferase (U/L) (mean [SE])				
Baseline	90.2 (11.59)	114.2 (17.24)	96.0 (16.13)	106.0 (11.87)
Change to Week 24	4.7 (5.84)	-36.7 (12.21)	-27.0 (19.42)	-32.1 (11.02)
Total bilirubin (µmol/L) (mean [SE])				
Baseline	53.3 (12.97)	52.2 (10.13)	57.0 (18.05)	54.4 (9.75)
Change to Week 24	-9.6 (15.16)	-23.7 (9.23)	-19.3 (13.62)	-21.7 (7.92)
Height z-scores (mean [SE])				
Baseline	-2.26 (0.34)	-1.45 (0.27)	-2.09 (0.37)	-1.74 (0.23)
Change to Week 24	-0.16 (0.10)	0.05 (0.11)	0.00 (0.16)	0.03 (0.09)
Mean difference vs. placebo (95% CI)[a]		0.32 (0.16) (0.00, 0.65)	0.15 (0.17) (-0.18, 0.48)	0.24 (0.14) (-0.05, 0.53)
Weight z-scores (mean [SE])				
Baseline	-1.52 (0.32)	-0.74 (0.27)	-1.19 (0.35)	-0.94 (0.21)
Change to Week 24	0.10 (0.10)	0.29 (0.11)	0.15 (0.12)	0.22 (0.08)
Mean difference vs. placebo (95% CI)[a]		0.28 (0.14) (-0.01, 0.57)	0.08 (0.15) (-0.22, 0.37)	0.18 (0.13) (-0.08, 0.44)

[a] Based on least squares means from a mixed model for repeated measures (MMRM) with baseline value as a covariate, and treatment group, visit, treatment-by-visit interaction, treatment-by-baseline interaction and stratification factors (PFIC type and age category) as fixed effects.

In the pooled phase 3 analysis, median duration of exposure across the 121 patients having received at least one dose of odevixibat was 102.2 weeks. 87 (72%) of the 121 patients received ≥72 weeks of treatment with odevixibat.

At week 24, 36% of patients were serum bile acids responders (N=112); this effect was sustained at week 72 when 44% were serum bile acids responders (N=85). Pruritus scores improved in a consistent fashion by 63.5% at week 24 (N=102) and 72.3% at week 72 (N=76).

The rate of serum bile acid responders at week 72 for patients with PFIC1 was 25% (7 of 28 patients), 49% (22 of 45) for PFIC2 and 67% (8 of 12) for patients with other types of PFIC. Positive pruritus assessments at the patient level over 72 weeks was similar in patients with PFIC1 (n=24) and PFIC2 (n=43), with response rates of 69% and 70%, respectively. In the subgroup of patients with other types of PFIC (PFIC3, PFIC 4, PFIC6 and episodic PFIC, n=9) 91% were responders.

Mean (SD) changes from baseline at week 72 in ALT, AST and total bilirubin in the pooled phase 3 group were -25.88 (119.18) U/L (n=78), -9.38 (69.279) U/L (N=79), and -25/65 (120.708) µmol/L (1.50 mg/dL) (n=79), respectively. Results for GGT were variable. Consistent and substantial improvement in growth was observed during longer term treatment with odevixibat. Mean height and weight z-scores improved to -1.26 and -0.75 at week 72, respectively, representing mean (SD) changes of 0.44 (0.705) (n=76) and 0.42 (0.762) (n=77), respectively.

Clinical trials in ALGS

The efficacy of Bylvay® in patients with ALGS was evaluated in two phase 3 trials. ALGS trial 1 (Study A4250-012) was a 24-week, randomised, double-blind, placebo-controlled trial conducted in 52 patients with a confirmed diagnosis of ALGS. Patients were randomised 2:1 to 120 mcg/kg/day odevixibat or

placebo and stratified by age at randomisation (< 10 years and ≥ 10 to < 18 years). Patients whose ALT was > 10 × ULN or total bilirubin > 15 × ULN at screening were excluded in ALGS Trial 1.

Patients who completed ALGS Trial 1 were eligible to enrol in ALGS Trial 2 (Study A4250-015), a 72-week open-label extension trial. Results were analysed for Trial 1, and pooled for Trials 1 and 2, representing 96 weeks of treatment for patients that completed treatment with odevixibat in both trials.

The primary endpoint in ALGS Trial 1 was change in scratching severity score from baseline to Month 6 (Weeks 21 to 24) based on the worst scratching score using an ObsRO instrument. Scratching was assessed once in the morning and once in the evening using a 5-point scale (0-4).

Change in serum bile acid levels from baseline to the average of Weeks 20 and 24 was the key secondary endpoint. Additional secondary endpoints included change from baseline to end of treatment in sleep parameters (assessed using a 5-point scale (0-4)), total cholesterol concentration and clinician assessment of xanthomas.

Median age (range) of the patients in ALGS Trial 1 was 5.45 (0.5 to 15.5) years; 51.9% were male and 82.7% were white. 92.3% of patients had the JAG1 mutation and 7.7% had the NOTCH2 mutation. At baseline, 98.1% of patients were treated with concomitant anti-pruritic medications, including UDCA (88.5%). Overall, 51 (98.1%) of the 52 patients had moderate hepatic impairment and 1 (1.9%) (placebo group) had severe hepatic impairment based on the Child-Pugh classification. Baseline mean (SD) eGFR was 158.65 (51.437) mL/min/1.73 m^2. Baseline mean (SD) ALT, AST, and total bilirubin were 173.7 (84.48) U/L, 167.0 (83.22) U/L, and 55.14 (47.911) µmol/L, respectively. Baseline mean (SD) scratching score (range: 0-4) and serum bile acids levels were similar in odevixibat-treated patients (2.80 [0.520] and 237.4 [114.88] µmol/L, respectively) and placebo-treated patients (3.01 [0.636] and 246.1 [120.53] µmol/L, respectively).

Table 6 presents the results of the change from baseline in average scratching score based on the ObsRO assessments to Month 6 (Weeks 21 to 24) and results of the change from baseline in serum bile acids to the average of Weeks 20 and 24.

Table 6: Comparison of key efficacy results for odevixibat vs. placebo over the 24-week treatment period (ALGS Trial 1)

	Placebo (N=17)	**Odevixibat 120 mcg/kg/day (N=35)**
Change from baseline in average scratching score[a] to Month 6 (Weeks 21 to 24) of treatment		
LS Mean (95% CI)[b]	-0.80 (-1.27, -0.33)	-1.69 (-2.04, -1.34)
LS Mean difference vs. placebo (95% CI)[b] Two-sided p-value[b]		-0.88 (-1.44, -0.33) 0.0025
Change from baseline in serum bile acid concentration (µmol/L) to the average of Weeks 20 and 24 of treatment		
LS Mean (95% CI)[b]	22.39 (-34.75, 79.52)	-90.35 (-1.33, -47.56)
LS Mean difference vs. placebo (95% CI)[b] Two-sided p-value[b]		-112.74 (-178.78, -46.69) 0.0012

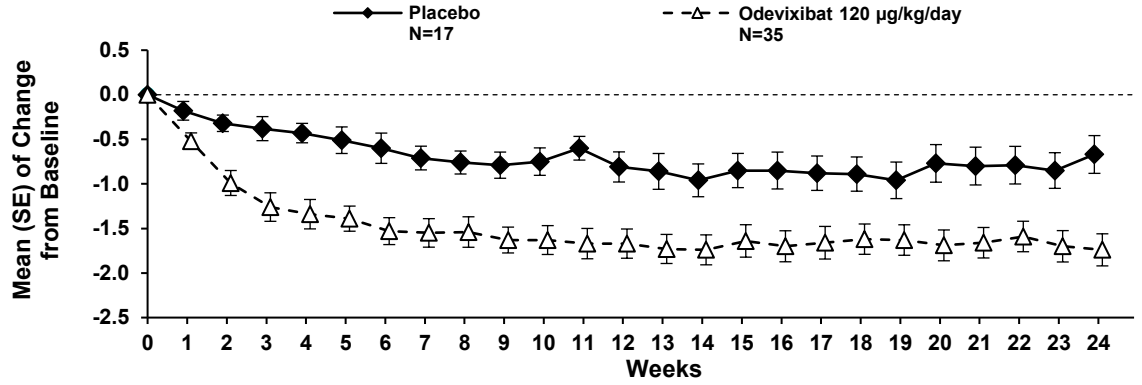
CI = confidence interval; LS Mean = Least Squares Means

[a] Based on the ObsRO instrument which is a validated 0-4 scale completed by caregivers (0=none to 4=very severe), where changes ≥1.0 have been shown to be clinically meaningful.

[b] The analyses are based on mixed-model effect repeated measures (MMRM) with baseline scratching score or baseline serum bile acid concentration (as applicable for the endpoint) as a covariate, and baseline age stratification (< 10, ≥ 10 years), baseline direct bilirubin (scratching score only), treatment group, time (months/visits), and treatment-by-time interaction as fixed effects.

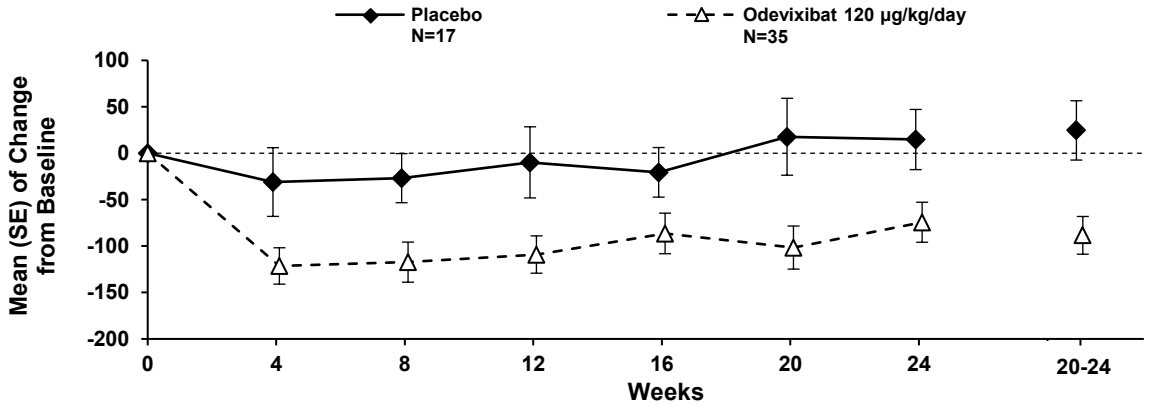
Figures 3 and 4 display graphically the mean changes (SE) from baseline of patients' average scratching scores in each treatment group for each week and patients' serum bile acid levels in each treatment group for each month, respectively.

Figure 3: Mean (± SE) change from baseline in pruritus (scratching) severity score over time (ALGS Trial 1)



Number of Patients																									
Placebo	17	17	17	16	17	17	17	17	17	17	16	16	16	15	15	16	15	16	17	17	16	16	16	17	16
120 µg/kg/day	35	34	35	34	34	35	35	33	34	34	34	34	34	34	33	33	34	35	35	35	33	34	35	33	31

Figure 4: Mean (± SE) change from baseline in serum bile acid concentration (µmol/L) over time (ALGS Trial 1)

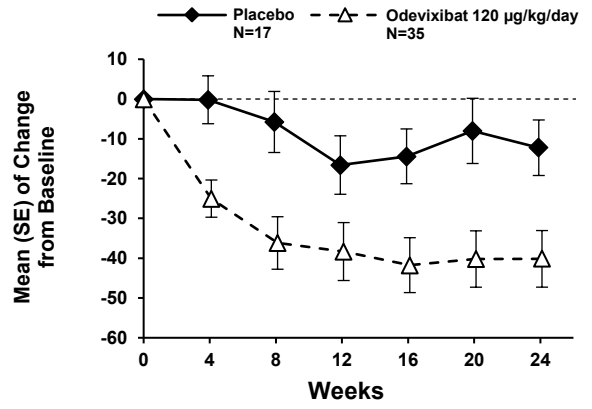


Number of Patients								
Placebo	17	16	15	16	17	15	16	17
120 µg/kg/day	35	34	35	35	35	35	33	35

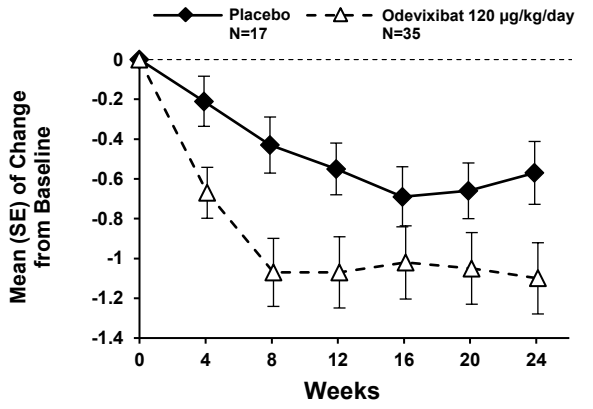
Consistent with the results for improvement in pruritus (scratching) severity, odevixibat led to improvements in multiple sleep parameters. Figure 5 displays graphically the mean changes (SE) from baseline for improvement in two of the sleep parameters by treatment group for each month, including percentage of days with help falling asleep and daytime tiredness score. Similar results were observed over time for percentage of days the child required soothing to go to sleep and the percentage of days the child slept with the caregiver.

Figure 5: Mean (±SE) change from baseline in sleep parameters over time (ALGS Trial 1)

Percentage of days with help falling asleep **Tiredness score**



Number of Patients							
Placebo	17	17	17	16	15	17	16
120 µg/kg/day	35	33	34	33	34	34	33



Number of Patients							
Placebo	17	17	17	16	15	17	16
120 µg/kg/day	35	34	34	34	33	35	34

Treatment with odevixibat led to mean improvement from baseline in serum cholesterol at Week 24. Least square mean (SE) changes from baseline in cholesterol levels were -0.91 (0.551) mmol/L and +0.67 (0.761) mmol/L in the odevixibat and placebo groups, respectively, with an LS mean difference (95% CI) of -1.59 (-3.43, 0.25). Treatment with odevixibat improved autotaxin levels over time, and some improvement was also seen in xanthomas.

A total of 44 (85%) of the 52 patients who received odevixibat across the Phase 3 studies completed the 72-week treatment period in Trial 2. Median duration of odevixibat treatment for the 52 patients across the pooled phase 3 studies was 99.79 weeks and ranged up to 2.5 years. Overall, 45 (87%) of the 52 patients had received >72 weeks of odevixibat with 32 (64%) having received > 96 weeks of treatment.

Continued treatment with odevixibat in ALGS Trial 2 led to further improvements in pruritus score with results for the pooled population at weeks 69-72 (n = 43) showing mean (SD) changes from baseline of -1.95 (0.838). For those 31 patients who received odevixibat in both Phase 3 studies and had data available for analysis, continued improvement was observed through Weeks 93-96 with mean (SD) change from baseline of -2.18 (0.876). The reduction in serum bile acid levels was maintained at week 72, when mean change from baseline was -119.4 µmol/L (-48.8 µg/mL; n = 44). Among those 30 patients who received odevixibat in both Phase 3 studies and had data available for analysis at week 96, change from baseline in serum bile acids levels was -123.9 µmol/L (-50.6 µg/mL).
Improvements in sleep parameters, serum cholesterol levels and xanthomas were maintained over long-term treatment.

5.2 Pharmacokinetic properties

Absorption
Odevixibat is minimally absorbed following oral administration; absolute bioavailability data in humans are not available, and estimated relative bioavailability is < 1.5%. Peak odevixibat plasma concentration (C_{max}) is reached within 1 to 5 hours.
Observed exposures in paediatric patients (age between 1.1 and 16.0 years; body weight from 5.6 to 55.2 kg) are limited to trough values; for the 120 mcg/kg/day dose the trough values were below the limit of detection for 88% of the samples in patients with mild hepatic impairment (Child-Pugh A) and for 43% of the samples in patients with moderate hepatic impairment (Child-Pugh B). The maximum observed trough concentrations in Child-Pugh A and B were 0.455 and 3.38 ng/mL, respectively. Simulated C_{max} values in a paediatric PFIC patient population for the 40 and 120 mcg/kg/day doses are 0.211 ng/mL and 0.623 ng/mL, respectively, and AUC values were 2.26 ng × h/mL and 5.99 ng × h/mL, respectively. Simulated C_{max} and AUC values for the 120 mcg/kg/day dose in a paediatric ALGS population were similar to PFIC. There is minimal accumulation of odevixibat following once-daily dosing.

Effect of food

Systemic exposure of odevixibat does not predict efficacy. Therefore, no dose adjustment for food effects is considered necessary. Concomitant administration of a high-fat meal (800 - 1000 calories with approximately 50% of total caloric content of the meal from fat) resulted in decreases of approximately 72% and 62% in C_{max} and AUC_{0-24}, respectively, compared to administration under fasted conditions. When odevixibat was sprinkled on apple sauce, decreases of approximately 39% and 36% in C_{max} and AUC_{0-24}, respectively, were observed compared to administration under fasted conditions. Taking into account the lack of PK/PD relationship and need for sprinkling the odevixibat capsule contents on food for younger children, odevixibat can be administered with food.

Distribution
Odevixibat is more than 99% bound to human plasma proteins.
The mean body weight adjusted apparent volumes of distribution (V/F) in paediatric patients for the 40 and 120 mcg/kg/day dose regimens are 40.3 and 43.7 L/kg, respectively. The V/F in a typical 70 kg subject is predicted to be 3338 L.
The mean volume of distribution (V/F) in ALGS patients is predicted to be 1160 L. The geometric mean body weight adjusted V/F for ALGS is 57.9 L/kg.

Biotransformation
Odevixibat is minimally metabolised in humans.

Elimination
Following administration of a single oral dose of 3000 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 body weight normalised apparent total clearances (CL/F) in paediatric PFIC patients for the 40 and 120 mcg/kg/day dose regimens are 26.4 and 23.0 L/kg/h, respectively. The CL/F in a typical 70 kg subject is predicted to be 2970 L/h, and the mean half-life is approximately 2.5 hours.

The mean apparent clearance (CL/F) in ALGS patients is predicted to be 212 L/h, and the mean half-life is approximately 4.75 hours. The geometric mean body weight adjusted CL/F for ALGS is 10.5 L/h/kg.

Linearity/non-linearity
The C_{max} and AUC_{0-t} increase with increasing doses in a dose-proportional manner; however due to the high interindividual variability of approximately 40%, it is not possible to estimate the dose proportionality accurately.

Pharmacokinetic/pharmacodynamic relationship(s)
Consistent with the mechanism and site of action of odevixibat in the gastrointestinal tract, no relationship between systemic exposure and clinical effects is observed.

Special populations
No clinically significant differences in the pharmacokinetics of odevixibat were observed based on age, sex or race.

Hepatic impairment
The majority of patients with PFIC and all patients with ALGS 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. No data are available for patients with severe hepatic impairment (Child-Pugh C).

Renal impairment
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 is expected to be small due to low systemic exposure and the fact that odevixibat is not excreted in urine.

In vitro studies
In *in vitro* studies, odevixibat did not inhibit CYPs 1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 at clinically relevant concentrations, but was shown to be an inhibitor of CYP3A4/5.

Odevixibat does not inhibit the transporters P-gp; breast cancer resistance protein (BCRP), organic anion transporter (OATP1B1, OATP1B3); organic anion transporter (OAT1, OAT3); organic cation transporter (OCT2), multidrug and toxin extrusion transporter 1 and 2K (MATE1 or MATE2-K).

Odevixibat is a substrate of gastrointestinal efflux transporter P-gp, but not of BCRP.

5.3 Preclinical safety data

Adverse reactions not observed in clinical trials, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Reproductive and developmental toxicity
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. ventricular diverticulum, small ventricle and dilated aortic arch). 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Microcrystalline cellulose
Hypromellose Ph.Eur

Capsule shell
Bylvay® 200 mcg and 600 mcg hard capsules
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)

Bylvay® 400 mcg and 1200 mcg hard capsules
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

Printing ink
Shellac Ph.Eur
Propylene glycol
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
The in-use shelf-life after first opening is 4 weeks at or below 30°C.

6.4 Special precautions for storage

Store in the original package in order to protect from light. Do not store above 30 °C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with a tamper evident, child resistant polypropylene closure.
Pack size: 30 hard capsules

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Manufactured by:
Patheon France
40 Boulevard De Champaret
Bourgoin-Jallieu, 38300
France

8. PRODUCT REGISTRATION HOLDER

Zuellig Pharma Sdn Bhd

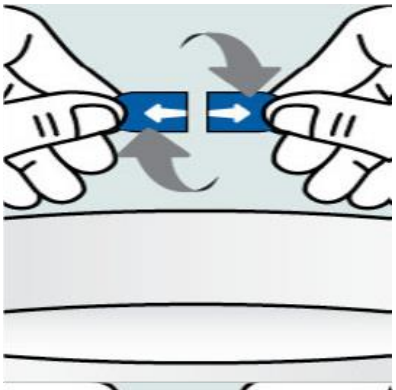
No. 15 Persiaran Pasak Bumi
Section U8, Perindustrian Bukit Jelutong
40150 Shah Alam, Selangor Darul Ehsan
Malaysia

9. REVISION DATE

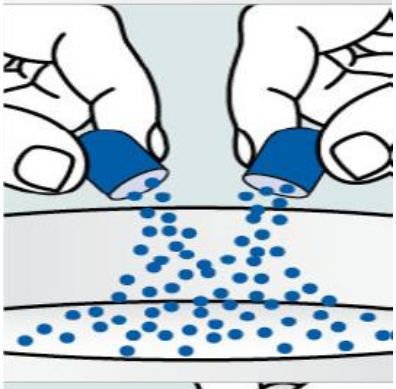
January 2026

Instructions to open capsules and sprinkle the contents on 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.

• Gently tap the capsule to ensure that all pellets come out

• Repeat the previous step if the dose requires more than one capsule.

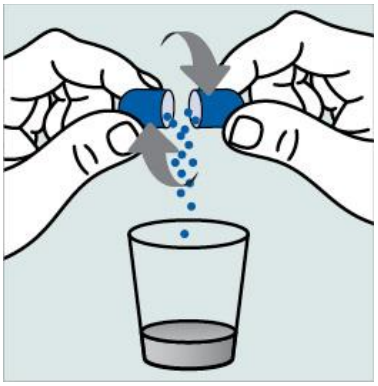
Step 4:
• Gently mix the contents of the capsule into the soft food.

• Take the entire dose immediately after mixing. Do not store the mixture for future use.
• Drink a glass of water following the dose.
• Dispose of the empty capsule shells.

Instructions to open capsules and sprinkle the contents in an age-appropriate liquid:

Do not administer via a bottle or “sippy cup” because the pellets will not pass through the opening. Pellets will not dissolve in liquids.

Contact your pharmacy if you do not have a suitable oral syringe for administration at home.

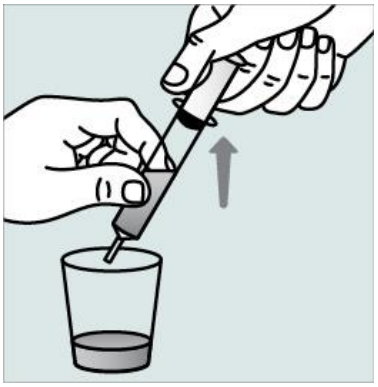


Step 1:
• Hold the capsule horizontally at both ends, twist in opposite directions.

• Pull apart and empty the contents into a small cup or glass. Gently tap the capsule to ensure that all pellets come out. Repeat this if the dose requires more than one capsule.

• Add 1 teaspoon (5 ml) of an age-appropriate liquid (e.g. breast milk, infant formula or water).

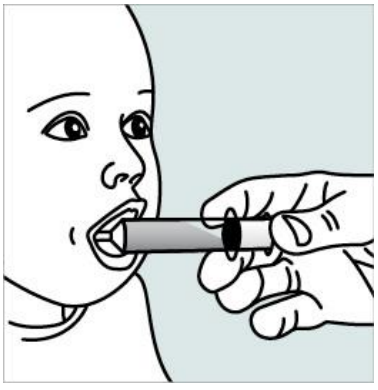
• Let the pellets sit in the liquid for approximately 5 minutes to allow complete wetting (pellets will not dissolve).



Step 2:
• 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.

Step 3:
• Withdraw the entire contents into the oral syringe by pulling the plunger on the end of the syringe.



Step 4:
• Place the tip of the oral syringe into the front of the child’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.

• If any pellet/liquid mixture remains in the mixing cup, repeat Step 3 and Step 4 until the entire dose has been administered.

• Give the entire dose immediately after mixing. Do not store the liquid/pellet mixture for future use.
• Give breast milk, infant formula or other age-appropriate liquid to drink following the dose.
• Dispose of the empty capsule shells.