

Annexe A

<u>Numéro EU</u>	<u>Nom (de fantaisie)</u>	<u>Dosage</u>	<u>Forme pharmaceutique</u>	<u>Voie d'administration</u>	<u>Conditionnement primaire</u>	<u>Présentation</u>
EU/1/21/1566/001	Bylvay	200 µg	Gélule	Voie orale	Flacon (PEHD)	30 gélules
EU/1/21/1566/002	Bylvay	400 µg	Gélule	Voie orale	Flacon (PEHD)	30 gélules
EU/1/21/1566/003	Bylvay	600 µg	Gélule	Voie orale	Flacon (PEHD)	30 gélules
EU/1/21/1566/004	Bylvay	1200 µg	Gélule	Voie orale	Flacon (PEHD)	30 gélules

Anhang A

<u>EU- Zulassungsnummer</u>	<u>Name (Phantasiebezeichnung)</u>	<u>Stärke</u>	<u>Darreichungsform</u>	<u>Art der Anwendung</u>	<u>Behältnis</u>	<u>Packungsgröße</u>
EU/1/21/1566/001	Bylvay	200 µg	Hartkapsel	Zum Einnehmen	Flasche (HDPE)	30 Kapseln
EU/1/21/1566/002	Bylvay	400 µg	Hartkapsel	Zum Einnehmen	Flasche (HDPE)	30 Kapseln
EU/1/21/1566/003	Bylvay	600 µg	Hartkapsel	Zum Einnehmen	Flasche (HDPE)	30 Kapseln
EU/1/21/1566/004	Bylvay	1200 µg	Hartkapsel	Zum Einnehmen	Flasche (HDPE)	30 Kapseln

Anexo A

<u>Número de procedimiento de la EU</u>	<u>Denominación (de fantasía)</u>	<u>Dosis</u>	<u>Forma farmacéutica</u>	<u>Vía de administración</u>	<u>Acondicionamiento primario</u>	<u>Tamaño del envase</u>
EU/1/21/1566/001	Bylvay	200 µg	Cápsula dura	Vía oral	Frasco (HDPE)	30 cápsulas
EU/1/21/1566/002	Bylvay	400 µg	Cápsula dura	Vía oral	Frasco (HDPE)	30 cápsulas
EU/1/21/1566/003	Bylvay	600 µg	Cápsula dura	Vía oral	Frasco (HDPE)	30 cápsulas
EU/1/21/1566/004	Bylvay	1200 µg	Cápsula dura	Vía oral	Frasco (HDPE)	30 cápsulas

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Bylvay 200 micrograms hard capsules
Bylvay 400 micrograms hard capsules
Bylvay 600 micrograms hard capsules
Bylvay 1 200 micrograms hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bylvay 200 mcg hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 200 micrograms odevixibat

Bylvay 400 mcg hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 400 micrograms odevixibat

Bylvay 600 mcg hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 600 micrograms odevixibat

Bylvay 1 200 mcg hard capsules

Each hard capsule contains odevixibat sesquihydrate equivalent to 1 200 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 1 200 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 or older (see sections 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology

The recommended dose of odeixibat is 40 mcg/kg administered orally once daily in the morning. Odeixibat can be taken with or without food.

Table 1 shows the strength and number of capsules that should be administered daily based on body weight to approximate a 40 mcg/kg/day dose.

Table 1: Number of Bylvay capsules needed to achieve the nominal dose of 40 mcg/kg/day

Body weight (kg)	Number of 200 mcg capsules		Number of 400 mcg capsules
4 to < 7.5	1	or	N/A
7.5 to < 12.5	2	or	1
12.5 to < 17.5	3	or	N/A
17.5 to < 25.5	4	or	2
25.5 to < 35.5	6	or	3
35.5 to < 45.5	8	or	4
45.5 to < 55.5	10	or	5
≥ 55.5	12	or	6

Capsule strength/number in **bold** is recommended based on predicted ease of administration.

Dose escalation

Improvement in pruritus and reduction of serum bile acid levels may occur gradually in some patients after initiating odeixibat 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 (see section 4.4.).

Table 2 shows the strength and number of capsules that should be administered daily based on body weight to approximate a 120 mcg/kg/day dose, with a maximum daily dose of 7 200 mcg per day.

Table 2: Number of Bylvay capsules needed to achieve the nominal dose of 120 mcg/kg/day

Body weight (kg)	Number of 600 mcg capsules		Number of 1 200 mcg capsules
4 to < 7.5	1	or	N/A
7.5 to < 12.5	2	or	1
12.5 to < 17.5	3	or	N/A
17.5 to < 25.5	4	or	2
25.5 to < 35.5	6	or	3
35.5 to < 45.5	8	or	4
45.5 to < 55.5	10	or	5
≥ 55.5	12	or	6

Capsule strength/number in **bold** is recommended based on predicted ease of administration.

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

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

No dose adjustment is required for patients with mild or moderate renal impairment.

There are no available clinical data for the use of odevixibat patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring haemodialysis (see section 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (see sections 5.1 and 5.2).

No data are available for PFIC patients with severe hepatic impairment (Child Pugh C). Additional monitoring for adverse reactions may be warranted in these patients when odevixibat is administered (see section 4.4).

Paediatric population

The safety and efficacy of odevixibat in children aged less than 6 months has not been established. No data are available.

Method of administration

Bylvay_{is} 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 food but may be swallowed whole.

The smaller 400 mcg and 1 200 mcg capsules are intended to be swallowed whole but may be opened and sprinkled on food.

If the capsule is to be swallowed whole, the patient should be instructed to take it with a glass of water in the morning.

For capsules to be opened, the patient should be instructed to:

- 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.
- 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.
- repeat the previous step if the dose requires more than one capsule.
- gently mix the pellets with a spoon into the soft food.
- administer the entire dose immediately after mixing. Do not store the mixture for future use.
- drink a glass of water following the dose.
- dispose 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,

e.g. patients with PFIC2 who have a complete absence or lack of function of Bile Salt Export Pump (BSEP) protein (i.e. patients with BSEP3 subtype of PFIC2) will not respond to odevixibat.

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

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section 5.2). Periodic liver function tests should be considered for patients with severe hepatic impairment.

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).

In clinical trials, increased levels in liver function tests were observed in some patients receiving odevixibat. Assessment of liver function 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.

For patients with liver function test elevations, more frequent monitoring should be considered.

Assessment of fat-soluble vitamin 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.

Treatment with odevixibat may impact the absorption of fat-soluble medicinal products, including lipophilic oral contraceptives (see sections 4.5 and 4.6).

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 7 200 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).

Cytochrome P450-mediated interactions

In vitro, odevixibat did not induce CYP enzymes (see section 5.2).

In *in vitro* studies, odevixibat 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.

No interaction studies have been conducted with UDCA and rifampicin.

No interaction studies have been conducted with oral hormonal contraceptives or other lipophilic medicinal products. It cannot be excluded that the absorption of oral contraceptives is affected by concomitant use of odevixibat.

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).

Paediatric population

No interaction studies have been performed in paediatric patients. No differences are expected between the adult and paediatric populations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception when treated with Bylvay. Since the uptake of lipophilic oral contraceptives may be affected by odeixibat, a barrier contraceptive method should be used (see section 4.4).

Pregnancy

There are no or limited data from the use of odeixibat 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.

Breast-feeding

It is unknown whether odeixibat or its metabolites are excreted in human milk. There is insufficient information on the excretion of odeixibat in animal milk (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

Summary of the safety profile

The most commonly reported adverse reaction was diarrhoea reported in (7%) of patients.

Tabulated list of adverse reactions

The table 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).

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

Table 3: Frequency of adverse reactions in PFIC patients

MedDRA system organ class	Common
Gastrointestinal disorders	diarrhoea, abdominal pain ^a , diarrhoea haemorrhagic, faeces soft
Hepatobiliary disorders	hepatomegaly

^aIncludes abdominal pain upper

Description of selected adverse reactions

Gastrointestinal adverse reactions

Gastrointestinal adverse reactions occurred at a frequency of 11% in patients treated with Bylvay. Adverse reactions of diarrhoea, abdominal pain and faeces soft were of short duration with most events ≤ 5 days in duration; median time to first onset was 16 days. All reports were mild to moderate in severity and non-serious. Two patients experienced an adverse reaction of clinically significant diarrhoea defined as diarrhoea that persisted for 21 or more days without any other aetiology, was severe in intensity, required hospitalisation or was considered an important medical event, or presented with concurrent dehydration requiring treatment with oral or intravenous rehydration and/or other treatment intervention (see section 4.4). Treatment interruption was reported for diarrhoea in 4% of patients and discontinuation of Bylvay due to diarrhoea was reported in 1%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

4.9 Overdose

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

The maximum dose administered to healthy subjects in clinical trials was odeixibat 10 000 mcg as a single dose, without any adverse consequences.

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

Odeixibat is a reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT).

Pharmacodynamic effects

Odeixibat 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

The efficacy of Bylvay in patients with PFIC was evaluated in two phase 3 trials. Trial 1 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 odeixibat and stratified by PFIC Type (1 or 2) and age (6 months to 5 years, 6 to 12 years, and 13 to \leq 18 years). Patients with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein and those with ALT $> 10 \times$ ULN or bilirubin $> 10 \times$ ULN were excluded. 13% of the patients had prior biliary diversion surgery. Patients completing Trial 1 were eligible to enrol in Trial 2, a 72-week open-label extension trial. The primary endpoint in Trial 1 was the proportion of patients with at least a 70% reduction in fasting serum bile acid levels or who achieved a level ≤ 70 μ mol/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/1.73 m². 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 odeixibat-treated patients (2.9 [0.089] and 252.1 [103.0] μ mol/L, respectively) and placebo-treated patients (3.0 [0.143] and 247.5 [101.1] μ mol/L, respectively).

Table 4 presents the results of the comparison of the key efficacy results in Trial 1 between odeixibat 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 in patients with 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				
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 ^a		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) ^b		28.23 (9.18) (9.83, 46.64)	21.71 (9.89) (1.87, 41.54)	24.97 (8.24) (8.45, 41.49)

^aBased on Cochran Mantel Haenszel test stratified by PFIC Type. P-values for the dose groups are adjusted for multiplicity.

^bBased 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 (\pm SE) change from baseline in serum bile acid concentration (μ mol/L) over time

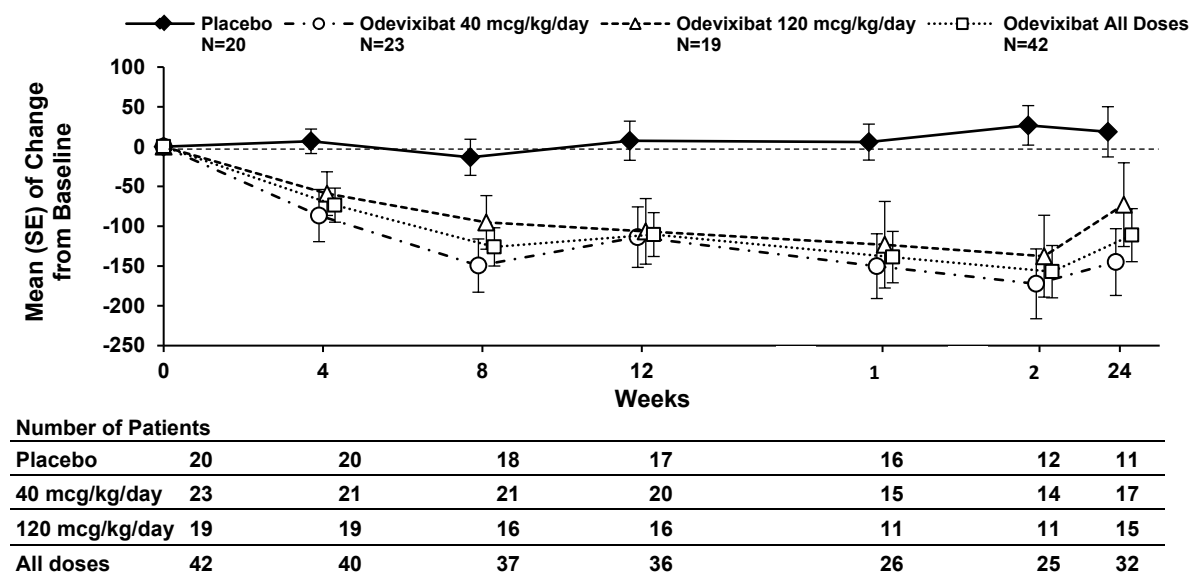
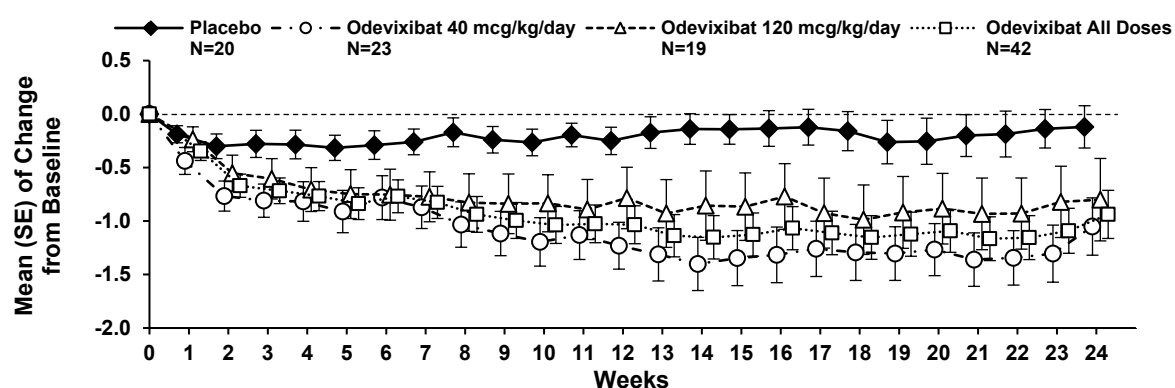


Figure 2: Mean (\pm SE) change from baseline in pruritus (scratching) severity score over time



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
40 mcg/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 mcg/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 line with 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 in patients with 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)
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)

^aBased 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.

Trial 2 is an interim cut of data from an ongoing 72-week open-label extension trial in PFIC patients treated with Bylvy 120 mcg/kg/day. The 79 patients (PFIC1 [22%], PFIC2 [51%], PFIC3 [5%] or PFIC6 [1%]) treated with 120 mcg/kg/day for up to 48 weeks experienced a durable effect on serum bile acids reduction, improvement in pruritus score, ALT, AST and total bilirubin. Across the 79 patients, 45 had assessments on or after 48 weeks of treatment with odevixibat, including 13, 30, 1 and 1 patients with PFIC1, PFIC2, PFIC3, and PFIC6, respectively; 9, 21, 4, and 0 patients, respectively, had not reached 48 weeks of treatment and were ongoing at the data cut-off. Overall, 7 patients with PFIC2 had discontinued prior to 48 weeks of treatment with odevixibat. Improvements in z-scores for height and weight indicate an enhanced growth velocity and the potential for catch-up growth in actively growing children.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Bylvy in paediatric population less than 6 months; see section 4.2 for information on paediatric use.

Exceptional circumstances

This medicinal product has been authorised under 'Exceptional Circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

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%. Peak odevixibat plasma concentration (C_{\max}) is reached within 1 to 5 hours. 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 \times h/mL and 5.99 ng \times h/mL, respectively. 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 - 1 000 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 AUC₀₋₂₄, respectively, compared to administration under fasted conditions. When odevixibat was sprinkled on apple sauce, decreases of approximately 39% and 36% in C_{\max} and AUC₀₋₂₄, 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.

Biotransformation

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 body weight normalised apparent total clearances CL/F in paediatric patients for the 40 and 120 mcg/kg/day dose regimens are 26.4 and 23.0 L/kg/h, respectively, and the mean half-life is approximately 2.5 hours.

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. Also, no dose-response relationship could be established for the investigated dose range 10-200 mcg/kg/day and the PD parameters C4 and FGF19.

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 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. Analysis of data from a placebo-controlled study in patients with PFIC Types 1 and 2 did not demonstrate a clinically important impact of mildly impaired hepatic function (Child Pugh A) on the pharmacokinetics of odevixibat. Although, body weight adjusted CL/F values were lower and body weight adjusted V/F values were larger in paediatric patients with PFIC with Child Pugh B compared to healthy subjects, the safety profile was comparable between the patient groups. Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

Renal impairment

There are no clinical data in patients with renal impairment, but the impact of renal impairment is expected to be small due to low systemic exposure and 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, OAT1, OAT3), organic cation transporter (OCT2), multidrug and toxin extrusion transporter (MATE1 or MATE2-K).

Odevixibat is not a BCRP substrate.

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 AUC₀₋₂₄). 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 AUC₀₋₂₄), 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 AUC₀₋₂₄), 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Hypromellose Ph.Eur

Capsule shell

Bylway 200 mcg and 600 mcg hard capsules
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)

Bylway 400 mcg and 1 200 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

6.4 Special precautions for storage

Store in the original package in order to protect from light. Do not store above 25 °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. MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden
e-mail: medinfo@albireopharma.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/001
EU/1/21/1566/002
EU/1/21/1566/003
EU/1/21/1566/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Almac Pharma Services Limited
Seagoe Industrial Estate
Portadown, Craigavon
County Armagh
BT63 5UA
United Kingdom (Northern Ireland)

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due data
<p>In order to investigate whether odevixibat treatment delays surgical biliary diversion (SBD) and/or liver transplantation (OLT), with matched comparison against untreated PFIC patients, the MAH should conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) according to an agreed protocol.</p>	<p>Annual interim reports are to be submitted along with the annual reassessments.</p>

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON FOR 200 MICROGRAMS****1. NAME OF THE MEDICINAL PRODUCT**

Bylvay 200 micrograms hard capsules
odevixibat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 micrograms odevixibat (as sesquihydrate).

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light. Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bylvay 200 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BOTTLE LABEL FOR 200 MICROGRAMS****1. NAME OF THE MEDICINAL PRODUCT**

Bylvay 200 micrograms hard capsules
odevixibat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 micrograms odevixibat (as sesquihydrate).

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light. Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON FOR 400 MICROGRAMS****1. NAME OF THE MEDICINAL PRODUCT**

Bylvay 400 micrograms hard capsules
odevixibat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 400 micrograms odevixibat (as sesquihydrate).

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light. Do not store above 25 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bylvay 400 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
BOTTLE LABEL FOR 400 MICROGRAMS**

1. NAME OF THE MEDICINAL PRODUCT

Bylvay 400 micrograms hard capsules
odevixibat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 400 micrograms odevixibat (as sesquihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light. Do not store above 25 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR 600 MICROGRAMS**

1. NAME OF THE MEDICINAL PRODUCT

Bylvay 600 micrograms hard capsules
odevixibat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 600 micrograms odevixibat (as sesquihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light. Do not store above 25 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bylvay 600 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
BOTTLE LABEL FOR 600 MICROGRAMS**

1. NAME OF THE MEDICINAL PRODUCT

Bylvay 600 micrograms hard capsules
odevixibat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 600 micrograms odevixibat (as sesquihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light. Do not store above 25 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR 1 200 MICROGRAMS**

1. NAME OF THE MEDICINAL PRODUCT

Bylvay 1 200 micrograms hard capsules
odevixibat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 1 200 micrograms odevixibat (as sesquihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light. Do not store above 25 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Bylvay 1 200 mcg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
BOTTLE LABEL FOR 1 200 MICROGRAMS**

1. NAME OF THE MEDICINAL PRODUCT

Bylvay 1 200 micrograms hard capsules
odevixibat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 1 200 micrograms odevixibat (as sesquihydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

hard capsule

30 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light. Do not store above 25 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/0/00/000/000

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Bylvay 200 micrograms hard capsules
Bylvay 400 micrograms hard capsules
Bylvay 600 micrograms hard capsules
Bylvay 1 200 micrograms hard capsules
odevixibat

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bylvay is and what it is used for
2. What you need to know before you take Bylvay
3. How to take Bylvay
4. Possible side effects
5. How to store Bylvay
6. Contents of the pack and other information

1. What Bylvay is and what it is used for

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, which 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.

Bylvay is used to treat 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.

2. What you need to know before you take Bylvay

Do not take Bylvay

- if you are allergic to odevixibat or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions

Talk to your doctor or pharmacist before taking Bylvay if you have:

- 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, or reduced circulation of bile acids between liver, bile and small intestine due to medicines, surgical procedures or diseases other than PFIC since these may reduce the effect of odevixibat

Talk to your doctor if you develop diarrhoea while taking Bylvay. Drinking sufficient liquid is recommended in patients with diarrhoea to prevent dehydration.

Increased levels in liver function tests can occur in some patients receiving Bylvay. Assessment of liver function is recommended for all patients prior to Bylvay treatment. Your doctor may recommend more frequent monitoring if you have elevated 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.

Other medicines and Bylvay

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. Treatment with odevixibat may affect the absorption of fat-soluble vitamins such as Vitamin A, D and E, and some medicines, including oral contraceptives.

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 of childbearing potential not using contraception. Use of a barrier contraceptive method is recommended since the uptake of lipophilic oral contraceptives may be affected by odevixibat.

It is not known if odevixibat 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, considering the benefit of breast-feeding to the baby and Bylvay to the mother.

Driving and using machines

Bylvay has no or negligible influence on the ability to drive or capacity to use machinery.

3. 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.

Treatment must be started and supervised by a doctor experienced in the management of progressive liver disease with reduced bile flow.

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.

The recommended dose is

- 40 micrograms odevixibat 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 odevixibat per kilogram body weight (up to a maximum of 7 200 micrograms once daily).

No dose differences are recommended for adults.

Method of use

Take the capsules once daily in the morning with or without food.

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

The larger 200 and 600 micrograms capsules are intended to be opened and sprinkled on food but may be swallowed whole.

The smaller 400 micrograms and 1 200 micrograms capsules are intended to be swallowed whole but may be opened and sprinkled on food.

Instructions to open capsules and sprinkle the contents on food:

- 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.



- Hold the capsule horizontally at both ends, twist in opposite directions.

- 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.

- 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.

If the medicine does not improve your condition after 6 months of continuous daily treatment, your doctor will recommend an alternative treatment.

If you take more Bylvay than you should

Tell your doctor if you think you have taken too much Bylvay.

Possible overdose symptoms are diarrhoea, stomach and bowel problems.

If you forget to take Bylvay

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

If you stop taking Bylvay

Do not stop taking Bylvay without first discussing with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects may occur with the following frequency:

common (may affect up to 1 in 10 people)

- diarrhoea, including diarrhoea with bloody stool, soft stools
- abdominal (belly) pain
- enlarged liver

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Bylvay

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

Store in the original package to protect from light. Do not store above 25 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Bylvay contains

- The active substance is odevixibat.
Each Bylvay 200 micrograms hard capsule contains 200 micrograms odevixibat (as sesquihydrate).
Each Bylvay 400 micrograms hard capsule contains 400 micrograms odevixibat (as sesquihydrate).
Each Bylvay 600 micrograms hard capsule contains 600 micrograms odevixibat (as sesquihydrate).
Each Bylvay 1 200 micrograms hard capsule contains 1 200 micrograms odevixibat (as sesquihydrate).

- Other ingredients are:

Capsule content

Microcrystalline cellulose
Hypromellose

Capsule shell

Bylvay 200 micrograms and 600 micrograms hard capsules
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)

Bylvay 400 micrograms and 1 200 micrograms hard capsules
Hypromellose
Titanium dioxide (E171)
Yellow iron oxide (E172)
Red iron oxide (E172)

Printing ink

Shellac
Propylene glycol
Black iron oxide (E172)

What Bylvay looks like and contents of the pack

Bylvay 200 micrograms hard capsules:

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

Bylvay 400 micrograms hard capsules:

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

Bylvay 600 micrograms hard capsules:

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

Bylvay 1 200 micrograms hard capsules:

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

Bylvay hard capsules are packed in a plastic bottle with a tamper evident, child resistant polypropylene closure. Pack size: 30 hard capsules.

Marketing Authorisation Holder

Albireo AB
Arvid Wallgrens backe 20
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Sweden
e-mail: medinfo@albireopharma.com

Manufacturer

Almac Pharma Services Limited
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County Armagh
BT63 5UA
United Kingdom (Northern Ireland)

This leaflet was last revised in

This medicine has been authorised under ‘exceptional circumstances’. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>.
There are also links to other websites about rare diseases and treatments.

Annex IV

Conclusions on the granting of the marketing authorisation under exceptional circumstances presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final evaluation document

**Odevixibat for treating progressive familial
intrahepatic cholestasis**

1 Recommendations

- 1.1 Odevixibat is recommended, within its marketing authorisation, as an option for treating progressive familial intrahepatic cholestasis (PFIC) in people 6 months and older. It is recommended only if the company provides odevixibat according to the commercial arrangement (see section 3).

Why the committee made these recommendations

PFIC is a rare and serious genetic condition that reduces or stops the flow of bile acids from the liver. This can cause severe pruritus (itching), poor growth and liver damage. PFIC severely affects the quality of life of people with the condition, and of their families and carers. It is fatal if untreated. Current treatment includes medicines not licensed for this condition (off label), then surgery such as an operation called partial external biliary diversion (PEBD) and, finally, a liver transplant.

Results from clinical trials suggest that, in people with the PFIC types 1 and 2, odevixibat reduces bile acid levels in the blood and pruritus compared with placebo (with or without off-label medicines). There is limited data for other types of PFIC. The clinical effectiveness of odevixibat when using the dose escalation schedule that would be used in NHS practice compared with PEBD is also uncertain.

The company's cost-effectiveness estimates are above what NICE usually considers acceptable for highly specialised technologies. However, several assumptions in the company's economic model are uncertain and possibly conservative, including:

- the percentage of people having odevixibat also having PEBD
- the average age at which treatment is started
- the reduction in quality of life from having a stoma bag
- death after a liver transplant.

When taking all these assumptions into account, the cost effectiveness of odevixibat is likely to be lower than the company's estimate. Also, the model does not capture:

- health-related benefits from delaying or stopping lifelong immunosuppression after a liver transplant
- the effect on quality of life for carers of people with PFIC
- the invasive nature of other treatments
- the young age at which PFIC can develop
- the innovative nature of odevixibat.

After taking all this into account, odevixibat is recommended for use in the NHS for PFIC.

2 The condition

- 2.1 Progressive familial intrahepatic cholestasis (PFIC) is the name given to a group of genetic disorders that affect the liver. They result in the flow of bile from the liver to the gastrointestinal tract being reduced or stopping completely. This causes bile to accumulate in the liver cells (cholestasis), which start to die and are replaced with scar tissue. This leads to cirrhosis (severe scarring) and liver failure. PFIC is caused by mutations in the genes that encode the proteins involved in transporting bile out of the liver, adversely affecting their function. Three main types have been identified. The most prevalent, PFIC2, is caused by mutations in the ABCB11 gene. PFIC1 is caused by mutations in the ATP8B1 gene and

PFIC3 by mutations in the ABCB4 gene. Rarer types, such as PFIC4, PFIC5 and PFIC6, have been identified. PFIC is typically inherited in an autosomal recessive pattern, meaning that 2 copies of the mutated gene (1 from each parent) must be present for it to develop. In PFIC1 and PFIC2, symptoms usually occur in the first months of life. PFIC3 can also appear later in infancy, in childhood or even during young adulthood. PFIC progresses at varying rates dependant on the type, but usually develops into cirrhosis within the first decade of life. It is fatal if untreated.

- 2.2 People with PFIC have a wide range of symptoms, determined primarily by the type they have. However, in all types, the condition is characterised by severe pruritus (itching), jaundice and raised serum bile acid levels. Diagnosis is primarily clinical. Other symptoms occurring outside the liver include diarrhoea, fat-soluble vitamin deficiencies and poor growth. These are more common in PFIC1. PFIC2 in particular is characterised by more rapid disease progression and a higher risk of liver cancer.
- 2.3 The prevalence of PFIC in England is unknown. However, worldwide estimates range between 1 per 50,000 to 1 per 100,000 live births. The marketing authorisation for odevixibat covers all types of PFIC.
- 2.4 There are no licensed medicines for PFIC. Initial management includes off-label medicines (for example, ursodeoxycholic acid, rifampicin, cholestyramine). The aim with these is to control the cholestatic pruritus. They are often given in combination and used alongside nutritional management, such as vitamin supplements to optimise nutrient absorption and promote growth. Surgical options are used when pruritus persists despite these off-label medicines. It includes surgical biliary diversion (SBD) and a liver transplant. Partial external biliary diversion is the most common form of SBD and involves diverting bile away from the gallbladder via an external stoma. A liver transplant is needed by most people with PFIC.

3 The technology

- 3.1 Odevixibat (Bylvay, Albireo Pharma) is a selective inhibitor of the ileal bile acid transporter (IBAT). IBAT is involved in the absorption of bile acids in the small intestine for circulation back to the liver. Odevixibat stops the recycling of bile acids, increasing their excretion through the colon and lowering hepatic and serum bile acid levels. It has a marketing authorisation under 'exceptional circumstances' for 'the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older'.
- 3.2 Odevixibat is administered daily as a capsule or sprinkled on food. The starting dose is 40 micrograms/kg/day up to a maximum dose of 222 micrograms/day based on a weight of 55.5 kg. After 3 months of continuous therapy, the dose may be escalated to 120 micrograms/kg/day if there has not been an adequate clinical response.
- 3.3 The adverse reactions listed in the summary of product characteristics for odevixibat include: diarrhoea, abdominal pain, soft stools and hepatomegaly (an enlarged liver). For full details of adverse reactions and contraindications, see the [summary of product characteristics](#).
- 3.4 Odevixibat is available as a pack of 30 capsules. The cost per pack of 200 microgram capsules is £2,620, per pack of 400 microgram capsules is £5,240, per pack of 600 microgram capsules is £7,860 and per pack of 1,200 microgram capsules is £15,720 (excluding VAT; company's evidence submission). The company has a commercial arrangement (a simple discount patient access scheme). This makes odevixibat available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

4 Consideration of the evidence

The evaluation committee (see section 8) considered evidence submitted by Albireo pharmaceuticals, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

- 4.1 Progressive familial intrahepatic cholestasis (PFIC) is a life-threatening condition. The patient experts highlighted that the complications of PFIC are multifaceted and significantly affect a child's development. The clinical experts stressed that, when PFIC is untreated, there is gradual loss of liver function, associated with pruritus and poor growth, which can be severe. The rate of progression can be rapid, especially for people with PFIC2. For this type, symptoms occur in newborns, and it often progresses to end-stage liver disease within the first few years of life. The clinical and patient experts stated that malnutrition, a lack of fat-soluble vitamins and the high bilirubin levels associated with cirrhosis can also affect neurological function. The committee concluded that PFIC is a complex and progressive condition, and that there are variations in symptoms and severity depending on the type.

Impact of the condition on people with PFIC and their families

- 4.2 The patient experts explained that the quality of life of a child with PFIC may be extremely poor. They emphasised that the pruritus can be debilitating, and that people can scratch themselves to the point of bleeding and skin damage. The patient experts stressed the profound nature of the pruritis, describing it as "itching from the inside out". Poor growth is a common concern for carers, particularly in PFIC1. The clinical

experts explained that children with PFIC eat a specific diet and take fat-soluble vitamin supplements to improve nutrient absorption. One patient expert highlighted that children may need a feeding tube to help manage the condition, which can be traumatic for the children as well as challenging for carers. Children with PFIC often have their education severely disrupted. This can be because of absence through illness and hospital attendances, and disrupted sleep impairing their ability to learn when at school. When compounded by condition-related learning disabilities, the educational attainment and social development of children with PFIC may be significantly affected. Carers explained that they needed to provide constant care to children with PFIC. Commonly, the demands are such that carers cannot work full time, resulting in loss of earnings and implications for career development. One carer explained that she could no longer carry on with her job as her daughter deteriorated, because of the demands of juggling hospital visits and sleepless nights. The patient experts stressed that a diagnosis of PFIC affects the entire family. Siblings can be affected by the large number of hospital visits and the experience of seeing a sibling suffer. The unpredictability of the condition, particularly the speed of progression, along with financial pressures can cause anxiety and other psychological difficulties for people with PFIC and their families. The committee concluded that PFIC has a significant effect on the quality of life of people with the condition, family members and carers.

Current management

- 4.3 The committee noted that there are no medicines licensed for PFIC in the UK. With medicines used off label, such as ursodeoxycholic acid, cholestyramine and rifampicin, the aim is to control the pruritus and delay progression to a liver transplant. However, response to off-label medicines varies, and there are no data from randomised controlled trials to support their clinical effectiveness. The clinical experts explained that cholestyramine is only commonly used in newborns because older

children find it hard to tolerate. Surgical options such as partial external biliary diversion (PEBD) are associated with a decrease in serum bile acid levels and increased native liver survival. However, the clinical experts explained that PEBD is rarely used in the NHS and is only an option in a limited group, for example, those who have no liver fibrosis and whose liver disease is not advanced. The committee heard that, for PEBD, an external stoma needs to be created. This can be distressing and can have a significant effect on quality of life. Also, with a stoma, there are risks of complications such as electrolyte disturbance, dehydration, bile leakage and other problems. The clinical experts explained that PEBD is often declined as a therapeutic option by individuals and families. This is because many of them perceive that the adverse effects outweigh the potential benefits. More recently adopted methods of surgical biliary diversion (SBD), such as an internal biliary drainage or internal ileal exclusion avoid the need for an external stoma bag. But there is a lack of data about their relative benefit. The clinical experts explained that these methods are generally used as a longer-term solution in people whose condition has responded to PEBD but do not want or cannot tolerate an external stoma bag. For people who do not have SBD, or when pruritus persists despite surgery, a liver transplant is the only remaining option.

- 4.4 The committee heard that a liver transplant is needed for most people with PFIC by age 20 years. This is because of liver disease and uncontrollable pruritus. The patient experts explained that a liver transplant can be successful in resolving pruritus, so significantly improving the quality of life for children with PFIC and their carers. However, transplants are associated with complications such as infection, increased risk of skin or liver cancer and life-threatening complications of graft rejection. Lifelong immunosuppression, frequent hospital visits, regular monitoring for rejection after transplants and the potential for recurrence of pruritus are big concerns for people with PFIC and their families. Consultation comments submitted after the first evaluation meeting stressed that a transplant can negatively affect a child's social development. This is

because of lost school days for surgery and the inability to participate in activities or careers associated with high risks of infection. The committee recognised that treatment options for PFIC are currently limited. It concluded that there was an unmet need for a new treatment for this condition.

- 4.5 The clinical experts explained that the current pathway of care for people with PFIC varies depending on the type. They explained that control of pruritus with off-label medicines such as ursodeoxycholic acid is more successful in people with PFIC3 than with PFIC1 and PFIC2. This means that people with PFIC3 are less likely to progress to surgery. They clarified that PEBD is most effective at reducing serum bile acid levels in PFIC2. However, long-term outcomes after the procedure, such as time to transplant, are uncertain because of a lack of data. The clinical experts highlighted that a liver transplant is less likely to be offered to people with PFIC1. This is because of the potential for lasting non-liver complications including severe diarrhoea and pancreatitis and the high risk of recurrent pruritus. The committee concluded that the current pathway of care for PFIC is largely determined by type.
- 4.6 The company has positioned odeixibat as a first-line treatment for PFIC. Because no active treatment is routinely commissioned in the NHS for PFIC, the committee agreed that standard care without odeixibat was the appropriate comparator, as listed in the NICE scope. The company considered this included SBD such as PEBD but did not include off-label medicines. This was because people having odeixibat could also have off-label medicines for symptom management and that these medicines have poor clinical effectiveness. The ERG noted that off-label medicines were included in the NICE scope and would form part of standard care without odeixibat. The clinical experts highlighted that, if odeixibat was approved, off-label medicines would be started in the time leading up to diagnosis being confirmed. They also pointed out that off-label medicines would be started in babies younger than 6 months, who are not included

in the marketing authorisation for odevixibat. The clinical experts confirmed that odevixibat would most likely be started in people having off-label medicines who had little or no drop in serum bile acid levels. They also stated that odevixibat would likely replace surgical options such as PEBD. However, they thought that PEBD was unlikely to be offered as a subsequent treatment for people whose condition did not respond to odevixibat. This was because both interventions work in similar ways by reducing the amount of bile acids in the gut available for reuptake. So, the likelihood of a response to PEBD in people whose condition does not respond to odevixibat is small. One clinical expert estimated that there would be no response in about 10% of people. The committee concluded that the comparators for odevixibat were off-label medicines and SBD, including PEBD, and that sequential use of odevixibat and PEBD is unlikely in NHS practice.

- 4.7 The patient and clinical experts highlighted that there is an unmet need for treatments specifically targeting PFIC. They emphasised that odevixibat has the potential to improve quality of life, remove the need for SBD and delay the time to transplant for people with PFIC. The committee heard that complete relief of pruritus would represent a successful treatment, but anything to reduce pruritus would be beneficial. The clinical experts noted the need for a treatment that, in addition, both improved growth and preserved liver function. The committee recalled that cholestyramine is effective at lowering serum bile acid levels, but that it can be poorly tolerated (see section 4.3). It concluded that people with PFIC and their families would welcome odevixibat as a treatment for the condition.

Impact of the new technology

Clinical trial evidence

- 4.8 The main clinical trial evidence for odevixibat came from a phase 3 completed randomised controlled trial, PEDFIC1, and an ongoing single-arm open-label extension study, PEDFIC2. These trials enrolled people

with a clinical diagnosis of PFIC1 or PFIC2 who had elevated serum bile acid levels and cholestatic pruritus:

- PEDFIC1 enrolled children 6 months and older, 23 of whom had odevixibat 40 micrograms/kg/day and 19 of whom had 120 micrograms/kg/day. A further 20 people had placebo. The follow-up period was 24 weeks.
- PEDFIC2 is an ongoing long-term follow-up study of PEDFIC1. It has enrolled 71 people who have had odevixibat 120 micrograms/kg/day. This includes 53 people in cohort 1 who had previously participated in PEDFIC1 (19 who had 40 micrograms/kg/day, 15 who had 120 micrograms/kg/day and 19 who had placebo) and 16 people in cohort 2. Cohort 2 includes people of any age who weighed over 5 kilograms with any type of PFIC who either had not met the eligibility criteria for PEDFIC1 or were eligible for enrolment after PEDFIC1 recruitment had been completed, so had not had odevixibat before. Interim data from week 24 analyses were available from a July 2020 data cut.

The company also provided evidence for odevixibat from a completed exploratory phase 2 study. This study enrolled 20 children with cholestatic pruritus of any cause, who were allocated to odevixibat at doses of 10, 30, 60, 100 or 200 micrograms/kg/day for 4 weeks. The committee noted the wide range of odevixibat doses and that only 10 people in the trial had PFIC (types 1, 2 or 3). The committee concluded that the PEDFIC1 and 2 studies were the most appropriate data sources for odevixibat.

Comparator clinical-effectiveness evidence

- 4.9 The committee first considered the clinical-effectiveness evidence for odevixibat compared with off-label medicines. It noted that most people in both the odevixibat and placebo arms of PEDFIC1 were having concurrent off-label medicines. So, it agreed that PEDFIC1 provided relevant comparative data because off-label medicines form part of

current standard care and are likely to be given alongside odeixibat in clinical practice. The company did not present any data comparing odeixibat with PEBD or other types of SBD. It explained that an indirect comparison is planned that will compare odeixibat with standard care both with and without SBD. Comparative clinical-effectiveness data in the company's model came from NAPPED. This was a natural history cohort study that included 130 people with PFIC1 and 264 people with PFIC2 having standard care. The median follow-up time was 4.1 years (range 1.5 to 12.3 years). During this time, 48% of people with PFIC1 and 23% with PFIC2 had SBD. The committee agreed no evidence had been presented to compare odeixibat with PEBD. It concluded that the most appropriate comparative data source available for off-label medicines was PEDFIC1.

Clinical trial outcomes

- 4.10 The primary outcome for PEDFIC1 for Europe and the rest of the world (RoW) was the proportion of people who had a reduction of at least 70% in the serum bile acid level from baseline or levels that reached 70 micromol/litre or less. The primary outcome for PEDFIC2 (Europe and RoW) was the change in serum bile acid levels from baseline over the treatment period. The primary outcome in the US for both PEDFIC1 and 2 was the proportion of positive pruritus assessments over the treatment period. The company measured this using a new observer-reported outcomes instrument (ObsRO) developed for this purpose. The ObsRO instrument captures scratching on a scale of 0 (representing no scratching) to 4 (representing the worst possible scratching) using twice-daily patient and carer questionnaires. A positive pruritus response is defined by the company as an observer-reported scratching score of 1 or below, or a reduction of 1 or more points from baseline. Both studies also collected data on changes in growth, liver function, health-related quality of life, and the number of people having surgery or liver transplants. The patient experts explained that a reduction in pruritus would have the

biggest effect on the quality of life of people with PFIC. The clinical experts explained that the relationship between serum bile acid levels and pruritus levels is complex, and that the 2 do not always correlate. Nonetheless, in general, lower serum bile acid levels are associated with improved pruritus and native liver survival. The patient experts highlighted that improvements in growth and liver function tests are important outcomes to people with PFIC. This is because they are generally associated with reduced pruritus, and improved sleep and quality of life. The committee concluded that the main outcomes important to clinicians and people with PFIC and their families were captured in the company's clinical trials.

Clinical trial results

- 4.11 In PEDFIC1, the proportion of positive pruritus assessments (a reduction of at least 70% in serum bile acid level from baseline or reaching 70 micromol/litre or less) compared with placebo after 24 weeks of treatment was statistically significantly greater in the odevixibat combined treatment arms (33%) than the placebo arm (0%). The results suggested a difference in response for people who had 40 microgram/kg/day of odevixibat compared with 120 microgram/kg/day, but this was not statistically significant. Also, the results were based on small patient numbers (the exact proportions are academic in confidence and cannot be reported here). There was a statistically significant greater proportion of positive pruritus assessments (using the ObsRO instrument) in people in PEDFIC1 who had odevixibat (all doses; 54%) compared with placebo (29%). For people who continued to have odevixibat in PEDFIC2, the improvement in serum bile acid levels and pruritus was maintained. However, the greatest improvements were seen in those people who had not had odevixibat before, that is, people who had placebo in PEDFIC1 or were newly enrolled. The results also suggested some additional serum bile acid response to the 120 microgram/kg/day dose in people whose condition did not respond to the 40 microgram/kg/day dose in PEDFIC1

(the exact proportions are academic in confidence and cannot be reported here). The committee noted that the PEDFIC2 data used to determine the response to up titration included 4 people with a follow up of only 24 weeks. Improvements in growth were also seen in PEDFIC1 for odevixibat compared with placebo and were maintained in people continuing odevixibat in PEDFIC2. The committee concluded that odevixibat was effective in reducing both serum bile acid level and pruritus in PFIC1 and PFIC2.

4.12 The committee next considered the clinical effectiveness of odevixibat by PFIC type. It recalled that, in PEDFIC1, only people with PFIC1 and 2 were enrolled. Serum bile acid response rates improved in both types, but the data suggested a potential difference in the response rates by type. However, the committee noted that patient numbers in the subgroups were small, that the trial had not been designed to detect a difference by type, and that no statistical comparisons by type had been done. The committee noted that 5 people in PEDFIC2 had PFIC3 and 1 had PFIC6. However, there was no data for odevixibat in PFIC4 and PFIC5, even though these are included in the marketing authorisation. At the last data cut, 80% (4 of 5) people with PFIC3 had a serum bile acid response according to the definition in PEDFIC2. At the second meeting, the committee noted that the reduction in serum bile acid levels seen in PEDFIC2 for PFIC6 was smaller than for other subtypes. This result was uncertain because it was based on results from 1 person. The committee concluded that subgroup analyses from PEDFIC2 suggested some serum bile acid reduction for all subtypes enrolled. However, it noted these results were based on small numbers, with very little evidence for PFIC types other than 1 and 2.

4.13 In PEDFIC1, the proportion of people who had a treatment-related adverse event was higher for odevixibat (33%, 14 of 32) than placebo (15%, 3 of 20). The committee noted that the proportion of people with

any adverse effect during the treatment period was high at 83% (35 of 42) in the odeixibat arm and 85% (17 of 20) in the placebo arm. However, no serious adverse events related to odeixibat were reported in the phase 2 study or PEDFIC1 and 2. The clinical experts explained that odeixibat is well tolerated in clinical practice. The main adverse events are gastrointestinal and may be alleviated in some people by using the lower starting dose. The company stated that no additional safety monitoring is needed for odeixibat, and there are no special precautions or warnings for its use. The committee concluded that odeixibat has an acceptable adverse event profile.

Generalisability of the evidence

- 4.14 The clinical experts considered that the evidence from PEDFIC1 and 2 was broadly generalisable to the population with PFIC seen in England. However, the committee was aware of several potential differences between the clinical trial populations and NHS clinical practice. To enrol in both PEDFIC1 and 2, people needed to have a serum bile acid level of 100 micromol/litre or more and an average pruritus score of 2 or more on the company's ObsRO instrument. The committee noted that 5 people in PEDFIC1 and 3 people in PEDFIC2 had been excluded because they met the pruritus eligibility criteria but did not have a high enough serum bile acid level. The committee recalled that the aim of treatment is to reduce pruritus, so these people would likely have treatment in clinical practice. PEDFIC1 also excluded people with a previous lack of response to ileal bile acid transporter inhibitors and SBD within 6 months. The ERG flagged that odeixibat may also be used in these people and that they were included in cohort 2 of PEDFIC2. At the second evaluation meeting, the committee noted that the average age in PEDFIC1 was 4.25 years. One clinical expert highlighted that, if odeixibat were recommended, clinicians would treat PFIC from diagnosis. They explained that PFIC1 and 2 are commonly diagnosed in people within the first few months of life. The committee recalled that odeixibat has a marketing authorisation for

treating PFIC in people aged 6 months and older. So, the population who had odevixibat in clinical practice may be younger than that included in the company's trials. The clinical experts theorised that, if PFIC was treated with odevixibat earlier, the response could be better than that reported in the trials, although data to support this is lacking. This was because the liver disease would be less advanced and fluid bile acid accumulation causing cholestasis could be prevented. So, there was a possibility that the clinical trial results underestimated odevixibat's treatment effect in clinical practice. The committee recognised that the population included in the company's trials may not fully reflect that in clinical practice. However, given the limited data available, it concluded that data from the full populations of PEDFIC1 and 2 were suitable for decision making.

- 4.15 The committee recalled that, at the week 24 data cut in PEDFIC2, the maximum treatment duration with odevixibat was 48 weeks. The ERG noted that changes in long-term outcomes (including survival, reduced transplant rates or delays to a liver transplant with odevixibat) would therefore not have been captured in the evidence base. The effect of treatment on serum bile acid level, pruritus and growth over a longer period was also unknown. The clinical experts explained that people would have odevixibat until they had a lack of response or intolerable side effects, which may be after many years. The committee concluded that the effect of odevixibat on long-term outcomes was uncertain.
- 4.16 The committee recalled that the company's main trial evidence was limited to PFIC1 and PFIC2, and that there was no data for many of the less prevalent types. One clinical expert emphasised the rarity of the condition, estimating that 10 people a year at most were diagnosed with the most common type, PFIC2, in her clinic. Given that PFIC4, PFIC5 and PFIC6 account for a small proportion of all diagnoses, it is unlikely that further data could be collected on the rarer types in clinical trials. The

committee agreed that the practical challenges of recruiting people with the rarer types of PFIC to clinical trials made data collection outside of the existing studies implausible. At the second evaluation meeting, the clinical experts stressed that odeixibat inhibits reuptake of bile acids in the colon. So, it is expected to work in all PFIC types with some bile flow out of the liver to the gut. People with PFIC2 with a bile salt export pump protein (BSEP) 3 mutation have a complete absence of the BSEP. So, their condition would not be expected to respond to treatment. However, the committee noted that people with a BSEP3 mutation were excluded from the marketing authorisation for odeixibat, so would not have treatment in the NHS. One clinical expert explained that odeixibat might not be effective in PFIC5. This is because it results in deficient BSEP protein expression and causes unregulated bile acid synthesis in the liver. Bile acid levels are so high that blocking reuptake in the intestine may not resolve the symptoms. The committee recalled that there was no clinical evidence available to show whether odeixibat did or did not work in PFIC5. It was also aware of the rare nature of this subtype (the company's response to consultation stated that, worldwide, the literature reports PFIC5 in 9 people). So, the number of people with PFIC5 in the NHS is extremely small. Finally, the committee was aware that the marketing authorisation recommended odeixibat for a general PFIC population. The committee concluded that there was limited data in the less prevalent subtypes of PFIC.

- 4.17 The committee recalled that the marketing authorisation for odeixibat specifies a starting dose of 40 micrograms/kg/day. The dose can be escalated to 120 micrograms/kg/day if there has not been an adequate clinical response after 3 months of continuous therapy. The clinical experts classed an adequate response to odeixibat as improvements in at least 2 of the 3 main PFIC outcomes: serum bile acid levels, pruritus and liver function tests. They acknowledged that a definition of response might vary among clinicians. However, they explained that the dose of

odevixibat would likely be increased if little or no improvement in these outcomes was seen. At the second evaluation meeting, the company agreed that this definition was likely to be used in clinical practice to determine the need for dose escalation. The ERG also stated that pruritus is the most clinically important outcome, so would primarily be used to assess response to treatment. The committee noted that the dosage of odevixibat given in the clinical trials was not based on response. People who had 40 micrograms/kg/day in PEDFIC1 and then went into PEDFIC2 had the high dose regardless of the previous response to treatment. Also, people enrolled in the PEDFIC2 cohort 2 started on high-dose odevixibat, whereas they would start on a lower dose in clinical practice. The clinical experts explained that the mechanism underlying response in PFIC was complex but expected the condition in some people to respond to dose escalation. The committee agreed that the dose of odevixibat would be escalated in people whose condition showed no improvement in at least 2 of serum bile acid levels, pruritus and liver function tests.

Cost to the NHS and value for money

Economic model for PFIC

- 4.18 The company developed a semi-Markov model to estimate the cost effectiveness of odevixibat. The population included in the model was limited to people with PFIC1 and PFIC2, reflecting evidence from the PEDFIC1 study. The model health states included response and loss of response for serum bile acid, response and loss of response to PEBD, a liver transplant, after a liver transplant and death. Only people who had odevixibat could have a serum bile acid response, which the company assumed was always associated with an improvement in pruritus. Following loss of response to odevixibat, people in the model did not have SBD, instead progressing straight to a liver transplant. People having standard care with off-label medicines were assumed not to have a serum bile acid response and entered the model in the serum bile acid loss-of-

response health state. They could then progress to a liver transplant from any of the loss-of-response health states, but not from the PEBD response state. Most people remained in the liver-transplant health state for 1 cycle only. However, a small proportion of people in both arms remained for an additional cycle to represent people who had another transplant. The company assumed that people moved up to the higher dose of odeixibat if there was no response after 6 months of continuous treatment at 40 micrograms/kg/day.

- 4.19 The clinical experts highlighted that the model did not capture treatment differences for other types of PFIC, for example, that people with PFIC3 are less likely to have SBD (see section 4.5). They also highlighted that improvements in growth and liver function were important outcomes to people with PFIC and their families but had not been included in the company's modelling. The company assumed that people entered the model at the age of 4.25 years (the average age in PEDFIC1). However, the committee recalled that people with PFIC1 and 2 may start treatment at a younger age in clinical practice. The ERG noted that the modelled age represented the average for all PFIC subtypes, some of which are not commonly diagnosed in newborns. However, it provided a scenario analysis in which people entered the model at a lower age of 3 years. The committee concluded that the basic model structure was appropriate for decision making, but that people may start odeixibat younger than assumed in the company's model.

Clinical evidence in the model

- 4.20 The company used data from PEDFIC1 to populate the patient characteristics and serum bile acid response to odeixibat for people having the 40 micrograms/kg/day dose in the economic model. The company calculated the proportion of people having high-dose odeixibat in the model using the ratio between the people with a response at the low dose and those with a response at any dose. For people having high-dose

odevixibat, the model used the serum bile acid response at week 24 in PEDFIC2 for people whose condition had not responded to low-dose odevixibat in PEDFIC1. The committee noted that the company's assumptions about high-dose odevixibat were calculated using data from few people. For example, week 24 data at the cut-off was only available to inform the response rates for 4 people whose condition did not respond to 40 micrograms/kg/day. At the second meeting, the clinical experts estimated that around 30% of people would have high-dose odevixibat in clinical practice. The committee noted that this proportion was similar to the assumption in the company model. It concluded that the company's assumptions about high-dose odevixibat were associated with uncertainty but acceptable for decision making.

- 4.21 In people whose condition had responded to odevixibat, the company modelled loss of serum bile acid and pruritus response using the stopping rate from PEDFIC2. The ERG noted that people in the PEDFIC2 study who stopped odevixibat did so because of adverse effects, not because of a lack of serum bile acid response. This meant that the loss-of-response rate is likely to be higher in clinical practice than that modelled by the company. The clinical experts explained that people would be keen to keep having odevixibat if it improved pruritus. They thought people would only likely stop treatment if they had unbearable side effects or progression of liver disease. For this reason, the stopping rate in clinical practice was likely to be low and was therefore comparable to that in PEDFIC2. One clinical expert estimated that about 30% of people would stop odevixibat over time. The committee concluded that further data on the long-term effectiveness of odevixibat would be useful.
- 4.22 For the standard care arm, the probabilities for having PEBD and subsequent progression to a liver transplant were taken from the NAPPED natural history study. The committee noted that NAPPED was a global study. This meant that the rates of SBD reported (48% of people

with PFIC1 and 23% with PFIC2) were likely higher than those in England, where this surgery is rarely done. The clinical experts highlighted that geographical variations in PEBD rates were due to differences in PFIC subtype prevalence and clinician preference. They estimated that, before the availability of odevixibat in a clinical trial, PEBD was used in around 25% to 30% of people with PFIC in the UK. The company assumed that, in 5% of people, the response to PEBD would be lost in each cycle. This was based on clinical advice to the company. This advice was that the loss of response for PEBD would be slightly higher than that for odevixibat because of the complications associated with surgery. At the second committee meeting, the clinical experts explained that if someone had had odevixibat, it was unlikely that they would go on to have PEBD. This is because response to any PFIC treatment depends on the liver retaining some ability to transport bile acids into the gut. When bile acid transport out of the liver becomes inadequate (because of uncorrected liver disease or loss of bile acid transport receptor expression), response is lost. Therefore, if odevixibat treatment eventually fails, PEBD is unlikely to be effective. The clinical experts explained that response to PEBD is unpredictable. The committee noted that, after consultation, the company and ERG base cases included PEBD in the odevixibat and standard care arms at the rate reported in the NAPPED study. It agreed that both the proportion of people who had PEBD and those whose condition subsequently lost response in the company's model were uncertain. It considered company and ERG scenarios that varied these parameters. For the standard care arm, in the absence of further data sources, the committee accepted the company's assumptions for PEBD. However, in the intervention arm, the committee concluded PEBD rates had been overestimated because people who had had odevixibat were unlikely to go on to have PEBD.

- 4.23 The company calculated the probability of a liver transplant in people who had not had PEBD in both arms using data from native liver survival

curves in NAPPED. The ERG flagged that this data included people whose condition both did and did not show a serum bile acid response to treatment. So, transplant rates for odevixibat would likely be higher than was modelled. In its base case, the ERG assumed equal rates of liver transplants in the health states for serum bile acid loss of response and PEBD loss of response. The committee concluded that, in the absence of further data sources, the ERG's probability of a liver transplant was most appropriate for people who had not had PEBD.

- 4.24 The company modelled mortality rates using a variety of sources, which applied to both the odevixibat and standard care arms in the model. For the acute post-transplant mortality rates (applied in the year of transplant in the model), the company used a meta-analysis of mortality rates from 10 PFIC studies reported in the literature. For the long-term mortality rates, applied in the model from the second year after transplant, the company used data from survival curves from 4 of these studies. It fitted an exponential distribution to this data. This gave an acute post-transplant mortality of 11.31% and a long-term post-transplant mortality of 1.94%. The ERG's analysis, which corrected several errors in the company model, and adjusted the meta-analysis output, produced an acute post-transplant mortality rate of 10.92% and long-term rate of 1.42%. The committee agreed with the ERG's corrections and considered its mortality rates most appropriate for decision making.
- 4.25 At consultation, the company provided scenario analyses that assumed higher rates of post-transplant mortality in people who had a second transplant compared with rates after a first transplant. The scenario analyses applied hazard ratios reported in a paper by Watt et al. (2010) to the proportion of people assumed to have a second transplant in the model. The paper reported a lower risk of death for people who had a second transplant within 1 year of the first transplant compared with

people having a transplant later than this. The company presented 2 scenarios:

- the first assumed that, after the first operation, all retransplants occurred within 1 year (applying a hazard ratio (HR) of 1.52 in the model for the first year only)
- the second assumed all retransplants occurred after 1 year (applying an HR of 4.79 from 2 years onwards).

The ERG noted that Watt et al. (2010) was based on liver transplants occurring between 1990 and 1994. So, the rates reported may not be relevant because retransplantation procedures have improved. It also highlighted inconsistencies in the reporting and statistical analyses. One clinical expert explained a retransplant is needed by 10% to 20% of people with a liver transplant for PFIC. Most of these are for people with a BSEP3 mutation (excluded from odeixibat's marketing authorisation). Also, most occur in the first 3 months after the initial operation because of surgical complications and infections. The clinical experts estimated mortality of about 50% within 1 year for people needing a second transplant. As time goes on, fewer people need a retransplant, but the individual risk of dying increases because retransplant becomes more difficult. This is because of scar tissue build up in the liver and PFIC-specific complications including fat deposits around the graft. The committee noted that these mortality rates were higher than those estimated by the ERG's clinical experts, who predicted an additional 30% mortality for retransplant at any timepoint. Although the committee had not identified retransplant mortality as an issue in the first meeting, it acknowledged that the risk of death after the second transplant was likely to be higher than the first. However, it considered that the true effect on mortality of a second transplant lay between the company's 2 scenarios because:

- the first scenario did not capture the increased risk of death from a later retransplant
- the second scenario did not capture that the increased chance of retransplant was mainly within the first year after initial surgery.

To account for this, the committee preferred to apply the higher hazard ratio of 4.79 to the proportion of people having more than 1 transplant, but only in the first year in the model.

Costs applied in the model

- 4.26 The company applied the costs of odevixibat in the serum bile acid response state and for 6 weeks in the first cycle of the serum bile acid loss-of-response health state. Dosing was based on the average weight by age up to a weight of 55.5 kilograms. The company also applied a normal distribution to calculate the proportion in each weight category. The costs of off-label medicines were included in the loss-of-response health states for both arms because the company assumed that they would be used alongside odevixibat. Because there were no serious adverse events related to odevixibat in PEDFIC1 and 2, the company did not include costs for adverse events in its base case. It did, however, include costs for carers' lost productivity for everyone younger than 18 years in the model. It stated that odevixibat was expected to have a cost saving beyond the NHS and personal social services (see section 4.37). The committee agreed with the ERG that the inclusion of productivity costs was outside the NICE reference case. It preferred the ERG's analyses, which excluded productivity costs and included costs for commonly occurring treatment emergent adverse events in PEDFIC1.
- 4.27 The committee noted uncertainty in the company's costs for PEBD. The ERG noted that the company's costs for PEBD included repeated surgeries for 67% of people, with equal costs applied to each surgery (same cost as initial procedure). The ERG stated that these assumptions were likely to be overestimates, so the cost of PEBD surgery in clinical

practice would likely be lower. The ERG presented a scenario that used lower costs for PEBD. The committee agreed that the company's costs were uncertain and considered both the company's base case and ERG's scenario in its decision making.

Utilities

- 4.28 PEDFIC1 and 2 collected Paediatric Quality of Life Inventory (PedsQL) data at baseline and week 24. This was mapped to EQ-5D-3L using a mapping algorithm from Khan et al. (2014). However, data was only available for a few people, so the company chose to use utility values from the literature in its base case. The company sourced utility values for odeixibat response from a study by Kamath et al. (2015). For loss of response, it used utility values of 0.91 from healthy children to represent serum bile acid response, and 0.83 from children with chronic intrahepatic cholestasis of any cause (of whom 51% had genetically confirmed PFIC). The ERG noted that, because of ongoing complications (including extra-hepatic features) and symptoms of PFIC, people whose condition has responded to odeixibat are unlikely to have the same quality of life as a healthy child. So, the company's utility values were higher than would be expected in clinical practice. The ERG preferred to use the utility values from the company's mapping study in its base case (0.858 for serum bile acid response and 0.697 for serum bile acid loss of response). The committee agreed that the company's utilities were likely to be high and that values derived directly from the clinical trial were preferred.
- 4.29 For response and loss of response to PEBD, the company used the utility for healthy children from Kamath et al. (2015). However, it applied a utility multiplier of 0.722 to represent the quality-of-life effect of having a stoma bag. This was taken from a study of adults with ulcerative colitis by Arseneau et al. (2006). For the PEBD loss-of-response health state, the company applied an additional disutility of 0.977 for short stature, reported in a study of children with chronic kidney disease by Al-Uzri et al. (2013).

This resulted in utilities of 0.659 for PEBD response and 0.599 for PEBD loss of response. The company also presented scenario analyses using a stoma bag utility multiplier of 0.945 from a colorectal cancer study by Hornbrook et al. (2011) and its own utility elicitation study (the exact value is academic in confidence and cannot be reported here). The committee noted that most people in the colorectal cancer study were over 70 years old, so it was unlikely to be comparable to the population with PFIC. It also heard that the company's vignette study only used data from 2 carers of children with PFIC, so was not considered sufficiently robust to capture all stoma bag-related issues by the ERG. At the first committee meeting, the ERG chose to use a disutility multiplier of 0.833 in its base case. This was calculated by averaging the disutilities derived from the colorectal cancer and ulcerative colitis studies, and was preferred by the committee at the time. However clinical expert feedback at consultation was that the disutility of a stoma bag for PEBD was expected to be comparable to that for ulcerative colitis. So, the ERG included the lower value of 0.722 in its updated base case. The clinical experts explained that the stoma-related effect on quality of life is significant, especially in older children. This is because the disutility may be larger for them compared with other age groups, and they often refuse an external biliary diversion. One clinical expert also highlighted that stoma-related quality of life was likely to be better for someone with colorectal cancer or ulcerative colitis than for someone with a stoma bag collecting bile. This is because the irritant nature of bile at the stoma site can cause problems including infection, which often needs treating with antibiotics and other interventions. At the second meeting, clinical experts also flagged the large volume of fluid loss with a PEBD stoma bag, sometimes up to 1 litre per day. In comparison, stoma bags for ulcerative colitis or colorectal cancer, which are located lower down the gastrointestinal tract, are associated with less fluid loss. The clinical experts agreed that literature utility multipliers from ulcerative colitis and colorectal cancer likely underestimated the quality-of-life effect of a stoma bag. One clinical expert stated that a utility multiplier derived

from an infant with a stoma bag for necrotising fasciitis, which also has a high volume of fluid loss, would be more comparable to a PEBD. At the first committee meeting, the patient experts highlighted that people with PFIC and carers have a very negative attitude to having a stoma bag, and that sometimes the invasive surgery may not resolve the pruritus. Consultation comments supported this view, describing a stoma bag as “a great discomfort” and “shameful” for people with PFIC. The committee agreed that the disutility of living with a stoma bag was likely to be lower than the utility multipliers derived from both the ulcerative colitis and colorectal cancer studies. It noted that the utility multiplier from the company’s elicitation study was considerably lower than the alternative values but recalled the small sample size informing the results. At the second meeting, the committee concluded that, in the absence of alternative sources, the utility multiplier derived from ulcerative colitis was most appropriate for decision making.

- 4.30 In the model, the company assumed that most people have a liver transplant did so because of uncontrolled pruritus. For this reason, both the company and ERG used a utility value of 0.710 in their base cases for liver transplantation, that was derived from people with severe pruritus. To represent the quality of life for people with PFIC post-transplant, the company used a value of 0.850, mapped from PedsQL data in a systematic review of children having a liver transplant. The ERG chose to use a lower value of 0.798 for this health state. There was no utility for after a liver transplant from the company’s mapping study. So, it calculated the ratio of the utilities for after a liver transplant and for odevixibat response from the literature. This ratio was then applied to the odevixibat response utility from the mapping study. The committee agreed that utilities mapped from the clinical trial were most appropriate. So, it concluded that the ERGs utility value for the post-liver-transplant health state were the most preferable.

- 4.31 The company and ERG included a carer disutility of -0.05 in the PEBD response, serum bile acid loss of response and post-liver-transplant health states and a disutility of -0.1 for the PEBD loss-of-response health state. The committee recalled that the burden on carers could be substantial because children with PFIC often needed a significant amount of carer support. However, it noted that the disutility for carers had been sourced from [NICE's technology appraisal guidance on nusinersen for treating spinal muscular atrophy](#) and on [dupilumab for treating moderate to severe atopic dermatitis](#). These conditions manifest in different ways to PFIC. The committee concluded that carer disutilities should be included in the modelling, but that the extent of any carer disutility in PFIC is uncertain.

Application of quality-adjusted life year (QALY) weighting

- 4.32 The committee understood that [NICE's interim process and methods of the highly specialised technologies programme](#) (2017) specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is seen through the number of additional QALYs gained and by applying a 'QALY weight'. It understood that a weight of between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. The committee considered that there was uncertainty in both the company's and ERG's analyses. However, it concluded that the undiscounted QALY gains for the scenarios incorporating its preferred assumptions did not meet the criteria for applying a QALY weight.

Cost-effectiveness analysis results

- 4.33 The company and NHS England have agreed a confidential commercial discount for odevixibat. All cost-effectiveness results of the economic analysis incorporating this discount, along with any comparator discounts, are confidential, so the ICERs cannot be reported here.
- 4.34 After consultation, the committee noted that the company's and ERG's updated base cases included the same assumptions. However, the ICER was above the threshold considered to provide value for money in the context of a highly specialised service when the confidential discounts for odevixibat and comparators were applied. The committee noted that the ERG's scenario using a start age of 3 years reduced the ICER. It also recalled that people were expected to start odevixibat in clinical practice at a younger age than that assumed in the company's model. Scenarios that assumed a higher mortality after a retransplant also lowered the ICER. The committee concluded that both the company's and ERG's base case cost-effectiveness results were likely higher than would be expected in clinical practice and that this ICER was likely to be conservative.
- 4.35 At the second committee meeting, the committee considered the following assumptions to be the most appropriate for decision making:
- including PEBD in the standard care arm only using rates from the NAPPED data
 - using a start age of 4.25 years (the average age in PEDFIC1), although it recognised the age might be lower than this (see section 4.19)
 - using the same probability of a liver transplant for odevixibat and PEBD loss-of-response health states
 - using the utility value from the ulcerative colitis study
 - using mortality rates for the acute and long term after a liver transplant from the ERG's analyses

- applying a hazard ratio of 4.79 in the first cycle only to the proportion of people with a second transplant
- excluding carer productivity costs
- including costs of common adverse events from PEDFIC1
- applying a 3.5% discount for costs and benefits, with no additional QALY weighting.

Using these assumptions, the cost-effectiveness results for odevixibat compared with standard care were considerably lower than the company's and ERG's base cases. However, they remained somewhat higher than the threshold normally considered an effective use of NHS resources in a highly specialised technology.

4.36 The committee also considered that there was some uncertainty surrounding the cost effectiveness of odevixibat for people with PFIC. The committee recognised that:

- it had been presented with very limited data for people with PFIC types other than PFIC1 and PFIC2
- there was no data for odevixibat when used before or compared directly with PEBD
- the long-term effectiveness of odevixibat on survival, time to a liver transplant and use of SBD was unclear
- the proportion of people whose condition stopped responding to treatment and the response rates to high-dose odevixibat were uncertain
- there was no evidence that used the dose escalation schedule in the marketing authorisation that would be used in NHS practice.

The committee acknowledged that some of these uncertainties could be resolved with data collection. It was aware that the PEDFIC2 study was ongoing and could provide further data on survival outcomes, liver transplant rates and alternative utility values for people having high-dose

odevixibat. It would also provide further data in PFIC3 and 6, including results for 2 additional people with PFIC6 currently unreported. The committee was aware that the company's planned indirect comparison would provide data on the effectiveness of odevixibat compared with PEBD. It also noted that a global registry had been requested by the regulator that:

- is expected to include some people from the UK
- would provide further data on the time to a liver transplant, SBD rates, survival and safety outcomes.

The committee concluded that additional data for odevixibat that would reduce the clinical-effectiveness uncertainty was expected in the near future.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.37 The company stated that odevixibat would result in benefits beyond those for the NHS and personal social services. The committee understood from the patient experts that children with PFIC need significant carer support, which can have a considerable effect on the quality of life of families. It recalled that carers frequently had to reduce their working hours or stop working because of the number of hospital visits and sleepless nights. The demands of caring for a child with PFIC after surgery or a transplant also needed large periods of time off work, which could have a severe financial impact on families. Carers also explained that living with immunosuppression after a liver transplant was extremely challenging for people with PFIC and their families. They highlighted the cost and resource use associated with frequent multiday hospitalisations and limitations to daily activities because of increased risk of illness. The committee considered that the full implications of immunosuppression may not have been fully captured in the model from an NHS and personal

perspective. The clinical experts stated that odevixibat could reduce the burden for families and carers because it had the potential to:

- lessen the number of hospital visits needed
- remove the need for an invasive SBD and associated stoma bag
- delay the time to a liver transplant.

Consultation comments after the first evaluation meeting stressed that supporting a child with PFIC has a significant effect on mental health. Also, it frequently causes depression and anxiety in carers of people with PFIC. Profound exhaustion for the whole family because of pruritus-related sleep deprivation is also common. Because there is evidence that odevixibat improved pruritus, it could lessen the psychological effect of the condition for people with PFIC, carers and siblings. A reduction in pruritus would also allow people with PFIC to attend school regularly, improving their education, career prospects and social skills. The committee noted that people with PFIC who have odevixibat would still:

- need to regularly monitor for signs of reduced liver function
- need to continue to eat an optimised diet to avoid malnutrition
- most likely still need a liver transplant at some point in their lives.

For these reasons, they would also most likely still need some support from carers. The committee recalled that the company and ERG had not applied carer disutilities in the serum bile acid response state (see section 4.31). So, people whose condition had responded to odevixibat were assumed to need less care than those in whom response had been lost. The committee agreed that PFIC affects people with the condition beyond the direct health benefits and that odevixibat had the potential to reduce the burden for carers. It concluded that the full disadvantages of the comparator treatments, and mental and physical effects on carers of people with PFIC may not have been fully captured in the company's modelling.

Delivery of specialised services

- 4.38 The company stated that treatment with odevixibat would be started and supervised by clinicians experienced in managing PFIC. It highlighted that the only additional monitoring needed with odevixibat is to determine response, and that no additional safety monitoring is needed. The committee noted that PFIC is currently managed in 3 specialist centres in England. The representative from NHS England confirmed that odevixibat would be started at specialist centres, with the potential to consider monitoring by local healthcare providers if safe and useful. The representative confirmed that additional infrastructure or staff training would not be needed to introduce odevixibat in England. The committee concluded that, if approved, odevixibat would be administered at specialist centres under the existing arrangements for people with PFIC.

Other factors

Innovation

- 4.39 The company stated that it considered odevixibat to be a step change in treating PFIC. This was because there are currently no licensed treatments for the condition, and current options have a high failure rate and can be invasive. The company highlighted that odevixibat is easy to administer in capsule form and can be sprinkled on to food for younger children. The clinical experts agreed that odevixibat was innovative because it is the first drug to both improve pruritus and limit progression of liver disease. They also flagged that the improvements in growth in people having odevixibat are important. The committee noted that odevixibat has a novel mechanism of action, no drug interactions and manageable side effects. It recalled that odevixibat was an oral drug that could remove the need for invasive PEBD and the trauma associated with a stoma bag. It also considered that surgical procedures such as a liver transplant and SBD were limited NHS resources that would be released if odevixibat were available. The committee recalled that there was high unmet need in

this population. It also noted that odeixibat statistically significantly reduced pruritus and serum bile acid levels in the randomised controlled trial compared with standard care. The committee recognised that odeixibat was innovative.

Equalities

- 4.40 The committee noted that the population for which odeixibat is indicated includes children and young people. It discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages. It noted [the principles that guide the development of NICE guidance and standards](#). This emphasises the importance of considering the distribution of health resources fairly within society as a whole, and factors other than relative costs and benefits alone. The committee acknowledged and considered the nature of the population as part of its decision making.

Conclusion

- 4.41 The committee recalled its earlier decisions and discussed the recommendation it could make for odeixibat for treating PFIC. It took into account the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits. The committee acknowledged that PFIC, and particularly pruritus, has a substantial effect on the quality of life of people with PFIC, and their carers and families. It noted that the clinical evidence suggested that odeixibat provides clinical benefit by reducing serum bile acid levels and pruritus compared with placebo. It recalled that there was no evidence presented for the rarer types of PFIC. It acknowledged the short follow-up period in the clinical trials, and the lack of data comparing odeixibat with PEBD and using the anticipated NHS dosing schedule. However, it noted that some of this uncertainty, such as time to, and need for, liver surgery and overall survival rates, could be reduced with data expected by the time of guidance review. The committee agreed that odeixibat likely reduces

serum bile acid levels and pruritus in people with PFIC. It concluded that some existing clinical-effectiveness uncertainties could be resolved with further data collection to be submitted at the guidance review stage.

- 4.42 The committee agreed that people would likely start odevixibat at a younger age in clinical practice than that modelled. The committee also considered that there were uncertainties associated with several parameters used in the model. This was particularly so for the size of the utility decrements associated with stoma bag use and caring for someone with PFIC. It agreed that a 3.5% discount rate for health and benefits with no additional QALY weighting was appropriate for decision making. When using the committee's preferred assumptions and applying the confidential discounts, the ICER was above what would normally be considered value for money within the context of a highly specialised service. However, the committee agreed that this base case was likely to be conservative.
- 4.43 The committee acknowledged that odevixibat is a high-cost technology and that uncertainties remained about the clinical evidence. It discussed the need to balance the importance of improving the lives of people with PFIC and their families. It noted [NICE's social value judgements: principles for the development of NICE guidance](#). This emphasises the importance of considering the distribution of health resources fairly within society as a whole, and factors other than relative costs and benefits alone. The committee recalled that PFIC1 and 2 are often diagnosed within the first 3 months of life. It concluded that the young age at which the condition develops should be considered in its decision making.
- 4.44 The committee agreed that some benefits of odevixibat were not fully captured in the company's modelling. These included the disadvantages of lifelong immunosuppression after a transplant and the quality-of-life decrement for carers. Taking account of the uncaptured benefits and that odevixibat is innovative, the committee concluded that odevixibat can be

considered a cost-effective use of NHS resources for highly specialised technologies.

4.45 The committee was aware of the uncertainty around the ICER for odevixibat. However, it acknowledged that there were additional factors that should be taken into consideration in its decision making, including:

- that PFIC affects the very young and that people would likely start odevixibat younger than was modelled (see section 4.19).
- the considerable effect on families and carers (see sections 4.2 and 4.37).
- the invasive nature of the current treatment options (see sections 4.3, 4.4 and 4.37).
- the innovative nature of odevixibat and health-related benefits not captured in the economic model (see sections 4.37 and 4.39).

The committee concluded that, considering all these factors, it was able to recommend odevixibat as an option for treating PFIC.

5 Implementation

5.1 Section 8(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation document.

- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has odevixibat and the doctor responsible for their care thinks that odevixibat is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for data collection

- 6.1 The committee noted an ongoing extension study, PEDFIC2, which uses odevixibat at a dose of 120 micrograms/kg/day and includes people with PFIC types 1, 2, 3 and 6. It also recalled that further data was expected from company's planned indirect treatment comparison with PEBD and the global registry study. These could resolve some of the uncertainty around odevixibat's treatment effect.
- 6.2 The committee noted that the following data would be useful at the time of the next guidance review:
- the ongoing effect of odevixibat on serum bile acid levels and pruritus, survival outcomes, liver transplant rates and alternative utility values for people having high-dose odevixibat in PEDFIC2
 - clinical effectiveness by PFIC subtypes from PEDFIC2, particularly types 3 and 6
 - the clinical effectiveness of odevixibat compared with PEBD from the company's indirect treatment comparison
 - UK specific data on starting age and stopping rates for odevixibat
 - alternative utility decrements for carers of people with PFIC and for having a stoma bag.

7 Date for review of guidance

- 7.1 The guidance on this technology will be considered for review 3 years after publication of the guidance, when final results from the ongoing extension study and indirect treatment analysis should be available. The

Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Paul Arundel

Chair, highly specialised technologies evaluation committee

January 2022

8 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

[Committee members](#) are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Emma Douch

Technical lead

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Technical adviser

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Project manager

ISBN: [to be added at publication]

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions (see section 4.8) for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Bylvay 200 micrograms hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains odevixibat sesquihydrate equivalent to 200 micrograms odevixibat

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

Size 0 capsule (21.7 mm × 7.64 mm) with ivory opaque cap and white opaque body; imprinted “A200” 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 or older (see sections 4.4 and 5.1).

4.2 Posology and method of administration

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

Posology

The recommended dose of odevixibat is 40 mcg/kg administered orally once daily in the morning. Odevixibat can be taken with or without food.

Table 1 shows the strength and number of capsules that should be administered daily based on body weight to approximate a 40 mcg/kg/day dose.

Table 1: Number of Bylvay capsules needed to achieve the nominal dose of 40 mcg/kg/day

Body weight (kg)	Number of 200 mcg capsules		Number of 400 mcg capsules
4 to < 7.5	1	or	N/A
7.5 to < 12.5	2	or	1
12.5 to < 17.5	3	or	N/A
17.5 to < 25.5	4	or	2
25.5 to < 35.5	6	or	3
35.5 to < 45.5	8	or	4
45.5 to < 55.5	10	or	5
≥ 55.5	12	or	6

Capsule strength/number in **bold** is recommended based on predicted ease of administration.

Dose escalation

Improvement in pruritus and reduction of serum bile acid levels may occur gradually in some patients after initiating odeixibat 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 (see section 4.4.).

Table 2 shows the strength and number of capsules that should be administered daily based on body weight to approximate a 120 mcg/kg/day dose, with a maximum daily dose of 7 200 mcg per day.

Table 2: Number of Bylvay capsules needed to achieve the nominal dose of 120 mcg/kg/day

Body weight (kg)	Number of 600 mcg capsules		Number of 1 200 mcg capsules
4 to < 7.5	1	or	N/A
7.5 to < 12.5	2	or	1
12.5 to < 17.5	3	or	N/A
17.5 to < 25.5	4	or	2
25.5 to < 35.5	6	or	3
35.5 to < 45.5	8	or	4
45.5 to < 55.5	10	or	5
≥ 55.5	12	or	6

Capsule strength/number in **bold** is recommended based on predicted ease of administration.

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

No dose adjustment is required for patients with mild or moderate renal impairment.

There are no available clinical data for the use of odevixibat patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring haemodialysis (see section 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (see sections 5.1 and 5.2).

No data are available for PFIC patients with severe hepatic impairment (Child Pugh C). Additional monitoring for adverse reactions may be warranted in these patients when odevixibat is administered (see section 4.4).

Paediatric population

The safety and efficacy of odevixibat in children aged less than 6 months has not been established. No data are available.

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 food but may be swallowed whole.

The smaller 400 mcg and 1 200 mcg capsules are intended to be swallowed whole but may be opened and sprinkled on food.

If the capsule is to be swallowed whole, the patient should be instructed to take it with a glass of water in the morning.

For capsules to be opened, the patient should be instructed to:

- 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.
- 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.
- repeat the previous step if the dose requires more than one capsule.
- gently mix the pellets with a spoon into the soft food.
- administer the entire dose immediately after mixing. Do not store the mixture for future use.
- drink a glass of water following the dose.
- dispose 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 odeixibat 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 odeixibat. For this reason, e.g. patients with PFIC2 who have a complete absence or lack of function of Bile Salt Export Pump (BSEP) protein (i.e. patients with BSEP3 subtype of PFIC2) will not respond to odeixibat.

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

Patients with severe hepatic impairment (Child-Pugh C) have not been studied (see section 5.2). Periodic liver function tests should be considered for patients with severe hepatic impairment.

Diarrhoea has been reported as a common adverse reaction when taking odeixibat. Diarrhoea may lead to dehydration. Patients should be monitored regularly to ensure adequate hydration during episodes of diarrhoea (see section 4.8).

In clinical trials, increased levels in liver function tests were observed in some patients receiving odeixibat. Assessment of liver function 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.

For patients with liver function test elevations, more frequent monitoring should be considered.

Assessment of fat-soluble vitamin 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.

Treatment with odevixibat may impact the absorption of fat-soluble medicinal products, including lipophilic oral contraceptives (see sections 4.5 and 4.6).

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 7 200 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).

Cytochrome P450-mediated interactions

In vitro, odevixibat did not induce CYP enzymes (see section 5.2).

In *in vitro* studies, odevixibat 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.

No interaction studies have been conducted with UDCA and rifampicin.

No interaction studies have been conducted with oral hormonal contraceptives or other lipophilic medicinal products. It cannot be excluded that the absorption of oral contraceptives is affected by concomitant use of odevixibat.

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).

Paediatric population

No interaction studies have been performed in paediatric patients. No differences are expected between the adult and paediatric populations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception when treated with Bylvay. Since the uptake of lipophilic oral contraceptives may be affected by odevixibat, a barrier contraceptive method should be used (see section 4.4).

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.

Breast-feeding

It is unknown whether odevixibat or its metabolites are excreted in human milk. There is insufficient information on the excretion of odevixibat in animal milk (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

Summary of the safety profile

The most commonly reported adverse reaction was diarrhoea reported in (7%) of patients.

Tabulated list of adverse reactions

The table 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).

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

Table 3: Frequency of adverse reactions in PFIC patients

MedDRA system organ class	Common
Gastrointestinal disorders	diarrhoea, abdominal pain ^a , diarrhoea haemorrhagic, faeces soft
Hepatobiliary disorders	hepatomegaly

^aIncludes abdominal pain upper

Description of selected adverse reactions

Gastrointestinal adverse reactions

Gastrointestinal adverse reactions occurred at a frequency of 11% in patients treated with Bylvay. Adverse reactions of diarrhoea, abdominal pain and faeces soft were of short duration with most events ≤ 5 days in duration; median time to first onset was 16 days. All reports were mild to moderate in severity and non-serious. Two patients experienced an adverse reaction of clinically significant diarrhoea defined as diarrhoea that persisted for 21 or more days without any other aetiology, was severe in intensity, required hospitalisation or was considered an important medical event, or presented with concurrent dehydration requiring treatment with oral or intravenous rehydration and/or other treatment intervention (see section 4.4). Treatment interruption was reported for diarrhoea in 4% of patients and discontinuation of Bylvay due to diarrhoea was reported in 1%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

The maximum dose administered to healthy subjects in clinical trials was odevixibat 10 000 mcg as a single dose, without any adverse consequences.

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).

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

The efficacy of Bylvay in patients with PFIC was evaluated in two phase 3 trials. Trial 1 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 $> 10 \times$ ULN or bilirubin $> 10 \times$ ULN were excluded. 13% of the patients had prior biliary diversion surgery. Patients completing Trial 1 were eligible to enrol in Trial 2, a 72-week open-label extension trial. The primary endpoint in Trial 1 was the proportion of patients with at least a 70% reduction in fasting serum bile acid levels or who achieved a level ≤ 70 $\mu\text{mol/L}$ 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/1.73 m². 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] $\mu\text{mol/L}$, respectively) and placebo-treated patients (3.0 [0.143] and 247.5 [101.1] $\mu\text{mol/L}$, respectively).

Table 4 presents the results of the comparison of the key efficacy results in 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 in patients with PFIC in trial 1

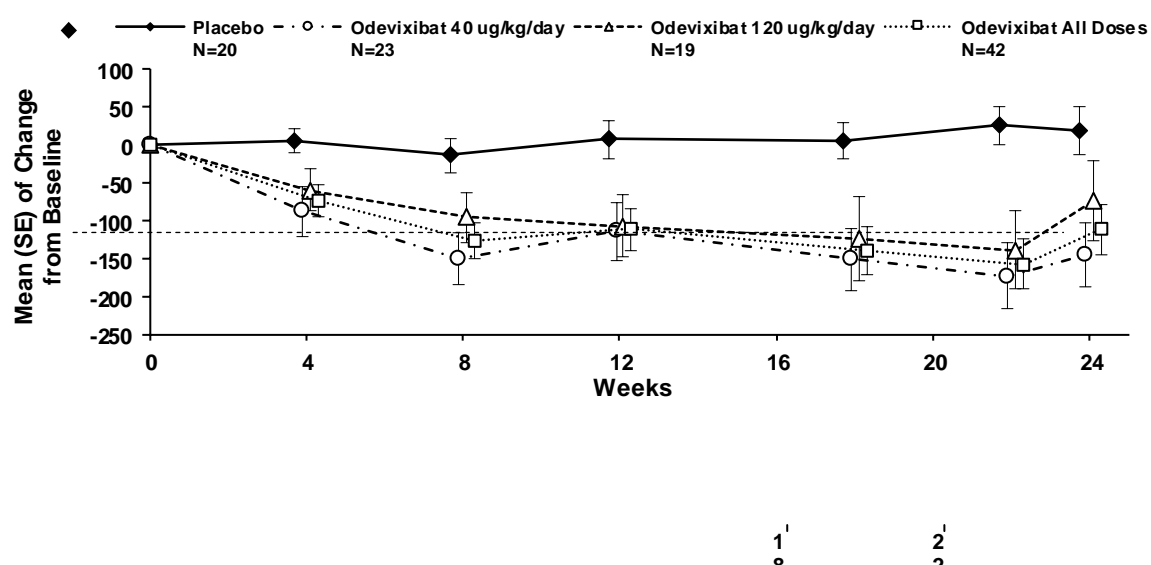
Efficacy endpoint	Placebo (N=20)	Odevixibat		
		40 mcg/kg/day (N=23)	120 mcg/kg/day (N=19)	Total (N=42)
Proportion of patients with reduction in serum bile acids at end of treatment				
n (%)	0 (0.00,	10 (43.5)	4 (21.1)	14 (33.3)

(95% CI)	16.84)	(23.19, 65.51)	(6.05, 45.57)	(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 ^a		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) ^b		28.23 (9.18) (9.83, 46.64)	21.71 (9.89) (1.87, 41.54)	24.97 (8.24) (8.45, 41.49)

^aBased on Cochran Mantel Haenszel test stratified by PFIC Type. P-values for the dose groups are adjusted for multiplicity.

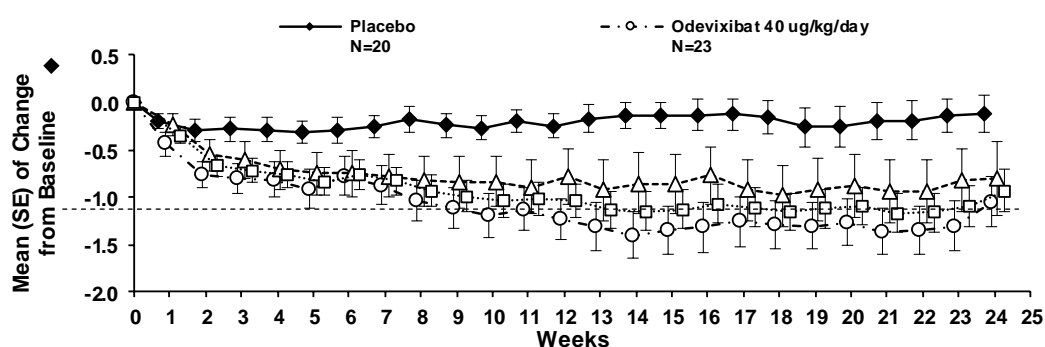
^bBased on least squares means from an analysis of covariance model with daytime and night-time baseline pruritus scores as covariates and treatment group and stratification factors (PFIC Type and age category) as fixed effects.

Figure 1: Mean (\pm SE) change from baseline in serum bile acid concentration (μ mol/L) over time



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

Figure 2: Mean (\pm 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	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	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	16	15	14
All doses	42	42	42	42	42	42	42	41	41	41	41	41	41	41	35	35	35	35	36	35	34	35	35	35	34	31

In line with 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 in patients with PFIC in trial 1

Efficacy endpoint	Placebo (N=20)	Odevixibat		
		40 mcg/kg/day	120 mcg/kg/day	Total

		(N=23)	(N=19)	(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)

^aBased 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.

Trial 2 is an interim cut of data from an ongoing 72-week open-label extension trial in PFIC patients treated with Bylvay 120 mcg/kg/day. The 79 patients (PFIC1 [22%], PFIC2 [51%], PFIC3 [5%] or PFIC6 [1%]) treated with 120 mcg/kg/day for up to 48 weeks experienced a durable effect on serum bile acids reduction, improvement in pruritus score, ALT, AST and total bilirubin. Across the 79 patients, 45 had assessments on or after 48 weeks of treatment with odevisibat, including 13, 30, 1 and 1 patients with PFIC1, PFIC2, PFIC3, and PFIC6, respectively; 9, 21, 4, and 0 patients, respectively, had not reached 48 weeks of treatment and were ongoing at the data cut-off. Overall, 7 patients with PFIC2 had discontinued prior to 48 weeks of treatment with odevisibat. Improvements in z-scores for height and weight indicate an enhanced growth velocity and the potential for catch-up growth in actively growing children.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Bylvay in paediatric population less than 6 months; see section 4.2 for information on paediatric use.

Exceptional circumstances

This medicinal product has been authorised under 'Exceptional Circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

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%. Peak odevixibat plasma concentration (C_{\max}) is reached within 1 to 5 hours. 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 $2.26 \text{ ng} \times \text{h/mL}$ and $5.99 \text{ ng} \times \text{h/mL}$, respectively. 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 - 1 000 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.

Biotransformation

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 body weight normalised apparent total clearances CL/F in paediatric patients for the 40 and 120 mcg/kg/day dose regimens are 26.4 and 23.0 L/kg/h, respectively, and the mean half-life is approximately 2.5 hours.

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. Also, no dose-response relationship could be established for the investigated dose range 10-200 mcg/kg/day and the PD parameters C4 and FGF19.

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 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. Analysis of data from a placebo-controlled study in patients with PFIC Types 1 and 2 did not demonstrate a clinically important impact of mildly impaired hepatic function (Child Pugh A) on the pharmacokinetics of odevixibat. Although, body weight adjusted CL/F values were lower and body weight adjusted V/F values were larger in paediatric patients with PFIC with Child Pugh B compared to healthy subjects, the safety profile was comparable between the patient groups. Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

Renal impairment

There are no clinical data in patients with renal impairment, but the impact of renal impairment is expected to be small due to low systemic exposure and 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, OAT1, OAT3), organic cation transporter (OCT2), multidrug and toxin extrusion transporter (MATE1 or MATE2-K).

Odevixibat is not a BCRP substrate.

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 AUC₀₋₂₄). 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 AUC₀₋₂₄), 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 AUC₀₋₂₄), 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Hypromellose Ph.Eur

Capsule shell

Hypromellose

Titanium dioxide (E171)

Yellow iron oxide (E172)

Printing ink

Shellac Ph.Eur

Propylene glycol

Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light. This medicinal product does not require any special temperature storage conditions.

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 MARKETING AUTHORISATION HOLDER

Albireo AB
Arvid Wallgrens backe 20
413 46 Göteborg
Sweden

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 36216/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/09/2021

10 DATE OF REVISION OF THE TEXT

07/09/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

BYLVAY (odevixibat) capsules, for oral use

BYLVAY (odevixibat) oral pellets

Initial U.S. Approval: 2021

INDICATIONS AND USAGE

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

Limitation of Use:

BYLVAY may not be effective in PFIC type 2 patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3).

DOSAGE AND ADMINISTRATION

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

Administration:

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

DOSAGE FORMS AND STRENGTHS

Oral Pellets: 200 mcg, 600 mcg (3)

Capsules: 400 mcg, 1200 mcg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Liver Test Abnormalities:** Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be required if abnormalities occur. For persistent or recurrent liver test abnormalities, consider treatment discontinuation. (5.1)
- Diarrhea:** Treat dehydration. Treatment interruption or discontinuation may be required for persistent diarrhea. (5.2)
- Fat-Soluble Vitamin (FSV) Deficiency:** Obtain baseline levels and monitor during treatment. Supplement if deficiency is observed. If FSV deficiency persists or worsens despite FSV supplementation, discontinue treatment. (5.3)

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause cardiac malformations (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

2.2 Preparation and Administration Instructions

2.3 Dose Modification for Management of Adverse Events

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Liver Test Abnormalities

5.2 Diarrhea

5.3 Fat-Soluble Vitamin (FSV) Deficiency

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

7.1 Bile Acid Binding Resins

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Limitations of Use

- BYLVAY may not be effective in PFIC type 2 patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

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

- BYLVAY oral pellets are intended for use by patients weighing less than 19.5 kilograms.
- BYLVAY capsules are intended for use by patients weighing 19.5 kilograms or above.

Table 1. Recommended Dosage for 40 mcg/kg/day

Body Weight (kg)	Total Daily Dose (mcg)
7.4 and below	200
7.5 to 12.4	400
12.5 to 17.4	600
17.5 to 25.4	800
25.5 to 35.4	1200
35.5 to 45.4	1600
45.5 to 55.4	2000
55.5 and above	2400

2.2 Preparation and Administration Instructions

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

Oral Pellets:

- Mix the contents of the shell containing oral pellet(s) into soft food. **Do not mix BYLVAY in liquids.**
- Do not swallow the shell containing oral pellets whole.
- Patients who are exclusively on liquid food should not use BYLVAY.

Administration Instructions:

1. Take BYLVAY in the morning with a meal.
2. Place a small amount of soft food (up to 30 mL [2 tablespoons] of apple sauce, oatmeal, banana or carrot puree, chocolate or rice pudding) in a bowl. Keep food at or below room temperature.
3. Open the shell containing oral pellet(s) and empty the contents into the bowl of soft food. Gently tap the oral pellet shell to ensure that all contents have been dispersed.
4. If the dose requires more than one shell of oral pellets, repeat step 2 and step 3.
5. Gently mix until well dispersed and administer the entire dose immediately.
6. Follow the dose with water.
7. Do not store mixture for future use.

Capsules:

Administration Instructions:

1. Take in the morning with a meal.
2. Swallow the capsule whole with a glass of water.
3. Alternatively, for patients unable to swallow the capsules whole, BYLVAY capsules may be opened, and sprinkled and mixed with a small amount of soft food. Follow directions above for oral pellets to prepare and administer such a mixture.

2.3 Dose Modification for Management of Adverse Events

Establish the baseline pattern of variability of liver tests prior to starting BYLVAY, so that potential signs of liver injury can be identified. Monitor liver tests (e.g., ALT [alanine aminotransferase], AST [aspartate aminotransferase], TB [total bilirubin], DB [direct bilirubin] and International Normalized Ratio [INR]) during treatment with BYLVAY. Interrupt BYLVAY if new onset liver test abnormalities occur or symptoms consistent with clinical hepatitis are observed [see *Warnings and Precautions* (5.1)].

Once the liver test abnormalities either return to baseline values or stabilize at a new baseline value, consider restarting BYLVAY at the lowest dose of 40 mcg/kg, and increase as tolerated if appropriate. Consider discontinuing BYLVAY permanently if liver test abnormalities recur.

Discontinue BYLVAY permanently if a patient experiences a hepatic decompensation event (e.g., variceal hemorrhage, ascites, hepatic encephalopathy).

3 DOSAGE FORMS AND STRENGTHS

Oral Pellets:

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

Capsules:

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Liver Test Abnormalities

Patients enrolled in the trial had abnormal liver tests at baseline. In Trial 1, treatment-emergent elevations of liver tests or worsening of liver tests relative to baseline values were observed during the clinical trial. Most abnormalities included elevation in AST, ALT, or total and direct bilirubin (see Table 2). Treatment interruption days ranged from 3 days to 124 days; none of the patients in Trial 1 permanently discontinued treatment due to liver test abnormalities [see *Adverse Reactions* (6.1)].

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

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

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

Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be required if abnormalities occur. For persistent or recurrent liver test abnormalities, consider treatment discontinuation [see *Dosage and Administration* (2.3)].

BYLVAY was not evaluated in PFIC patients with cirrhosis. Closely monitor for liver test abnormalities; permanently discontinue BYLVAY if a patient progresses to portal hypertension or experiences a hepatic decompensation event.

5.2 Diarrhea

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

If diarrhea occurs, monitor for dehydration and treat promptly. Interrupt BYLVAY dosing if a patient experiences persistent diarrhea. Restart BYLVAY at 40 mcg/kg/day when diarrhea resolves, and increase the dose as tolerated if appropriate. If diarrhea persists and no alternate etiology is identified, stop BYLVAY treatment.

5.3 Fat-Soluble Vitamin (FSV) Deficiency

Fat-soluble vitamins (FSV) include vitamin A, D, E, and K (measured using INR levels). PFIC patients can have FSV deficiency at baseline. BYLVAY may affect absorption of fat-soluble vitamins. In Trial 1, new onset or worsening of existing FSV deficiency was reported in 1 (5%) placebo-treated patient, and 3 (16%) BYLVAY-treated 120 mcg/kg/day patients; none of the BYLVAY-treated 40 mcg/kg/day patients had new onset or worsening of existing FSV deficiency [see *Adverse Reactions* (6.1)].

Obtain serum FSV levels at baseline and monitor during treatment, along with any clinical manifestations. If FSV deficiency is diagnosed, supplement with FSV. Discontinue BYLVAY if FSV deficiency persists or worsens despite adequate FSV supplementation.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

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

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

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

Table 3. Clinical Adverse Reactions in Trial 1

Preferred Term	Placebo N=20 n (%)	BYLVAY 40 mcg/kg/day N=23 n (%)	BYLVAY 120 mcg/kg/day N=19 n (%)	Total BYLVAY N=42 n (%)
Any AE	17 (85.0)	19 (82.6)	16 (84.2)	35 (83.3)
Diarrhea	2 (10.0)	9 (39.1)	4 (21.1)	13 (31.0)
Transaminases increased (ALT, AST)	1 (5.0)	3 (13.0)	4 (21.1)	7 (16.7)
Vomiting	0	4 (17.4)	3 (15.8)	7 (16.7)
Abdominal pain	0	3 (13.0)	3 (15.8)	6 (14.3)
Blood bilirubin increased	2 (10.0)	3 (13.0)	2 (10.5)	5 (11.9)
Fat-soluble vitamin deficiency (A, D, E)	1 (5.0)	0	3 (15.8)	3 (7.1)
Splenomegaly	0	0	2 (10.5)	2 (4.8)
Cholelithiasis	0	0	1 (5.3)	1 (2.4)
Dehydration	0	0	1 (5.3)	1 (2.4)
Fracture	0	1 (4.3)	0	1 (2.4)

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

7 DRUG INTERACTIONS

7.1 Bile Acid Binding Resins

Administer bile acid binding resins (e.g., cholestyramine, colesevelam, or colestipol) at least 4 hours before or 4 hours after administration of BYLVAY [see *Dosage and Administration* (2.2)]. Bile acid binding resins may bind odeixibat in the gut, which may reduce BYLVAY efficacy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

Odevixibat has low absorption following oral administration, and breastfeeding is not expected to result in exposure of the infant to BYLVAY at the recommended doses [see *Clinical Pharmacology* (12.3)]. There are no data on the presence of odevixibat in human milk, the effects on the breastfed

infant, or the effects on milk production. BYLVAY may reduce absorption of fat-soluble vitamins [see *Warning and Precautions* (5.3)]. Monitor FSV levels and increase FSV intake, if FSV deficiency is observed during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BYLVAY and any potential adverse effects on the breastfed child from BYLVAY or from the underlying maternal condition.

8.4 Pediatric Use

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

The safety and effectiveness of BYLVAY for the treatment of pruritus in PFIC in pediatric patients less than 3 months of age have not been established.

8.5 Geriatric Use

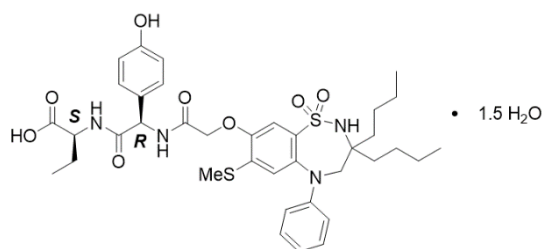
The safety and effectiveness of BYLVAY for the treatment of pruritus in PFIC in adult patients, including those 65 years of age and older, have not been established.

8.6 Hepatic Impairment

Patients with PFIC may have impaired hepatic function at baseline. The efficacy and safety in PFIC patients with clinically significant portal hypertension and in patients with decompensated cirrhosis have not been established [see *Clinical Studies* (14), *Dosage and Administration* (2.3), and *Warning and Precautions* (5.1)].

11 DESCRIPTION

The active ingredient in BYLVAY (odevixibat) capsules and BYLVAY (odevixibat) oral pellets, an ileal bile acid transporter (IBAT) inhibitor, is (2S)-2-([(2R)-2-(2-([3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1λ⁶,2,5-benzothiadiazepin-8yl]oxy)acetamido)-2-(4-hydroxyphenyl)acetyl]amino)butanoic acid, which is formulated as the sesquihydrate having the following chemical structure:



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

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Odevixibat is a reversible inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids (primarily the salt forms) from the terminal ileum.

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

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

Absorption

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

Sprinkle on Applesauce

When odevixibat 9.6 mg was administered after sprinkling the pellets on applesauce, decreases of 39% and 35% in C_{\max} and AUC_{0-24h} , respectively, and delayed median T_{\max} from 3 hours to 4.5 hours were observed compared to administration of whole capsules (eight 1200 mcg capsules) under fasted conditions. The effect of sprinkling on soft food on systemic exposure is not clinically significant [see *Dosage and Administration* (2)].

Effect of Food

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

Distribution

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

Elimination

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

Metabolism

In vitro, odevixibat was metabolized via mono-hydroxylation.

Excretion

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

Drug Interaction Studies

Effect of Other Drugs on Odevixibat

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

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

Effect of Odevixibat on Other Drugs

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

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

14 CLINICAL STUDIES

The efficacy of BYLVAY was evaluated in Trial 1 (NCT03566238), a 24-week, randomized, double-blind, placebo-controlled trial. Trial 1 was conducted in 62 pediatric patients, aged 6 months to 17 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-function or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal (ULN), or who had received a liver transplant were excluded in Trial 1.

Patients were randomized to placebo (n=20), 40 mcg/kg (n=23), or 120 mcg/kg (n=19). Study drug was administered once daily with a meal in the morning. In patients weighing less than 19.5 kg or patients who could not swallow the whole capsule, study drug was sprinkled on soft food and then administered orally.

Median age (range) of the patients in Trial 1 was 3.2 (0.5 to 15.9) years; 3 patients were older than 12 years of age. Of the 62 patients, 50% were male and 84% were white; 27% had PFIC type 1, and 73% had PFIC type 2. The mean (standard error [SE]) scratching score in the 2 weeks prior to baseline was 2.9 (0.08). Baseline mean (SE) eGFR was 164 (30.6) mL/min/1.73 m². Baseline median (range) ALT, AST, and total bilirubin were 65 (16-798) U/L, 83.5 (32-405) U/L, and 2.2 (0.2-18.6) mg/dL, respectively.

In Trial 1, a total of 13 patients discontinued from trial prematurely either due to no improvement in pruritus (n=11) or due to adverse reactions (n=2); 5/20 (25%) patients discontinued from the placebo arm and 8/42 (19%) patients discontinued from the BYLVAY arms. A total of 11 of the 13 patients rolled over to Trial 2 to receive BYLVAY 120 mcg/kg/day. One patient treated with BYLVAY 120 mcg/kg/day withdrew from the trial due to a treatment-emergent adverse event of diarrhea [see *Adverse Reactions* (6)].

Given the patients' young age, a single-item observer-reported outcome (ObsRO) was used to measure patients' scratching as observed by their caregiver twice daily (once in the morning and once in the evening). Scratching was assessed on a 5-point ordinal response scale, with scores ranging from 0 (no scratching) to 4 (worst possible scratching). Patients were included in Trial 1 if the average scratching score was greater than or equal to 2 (medium scratching) in the 2 weeks prior to baseline.

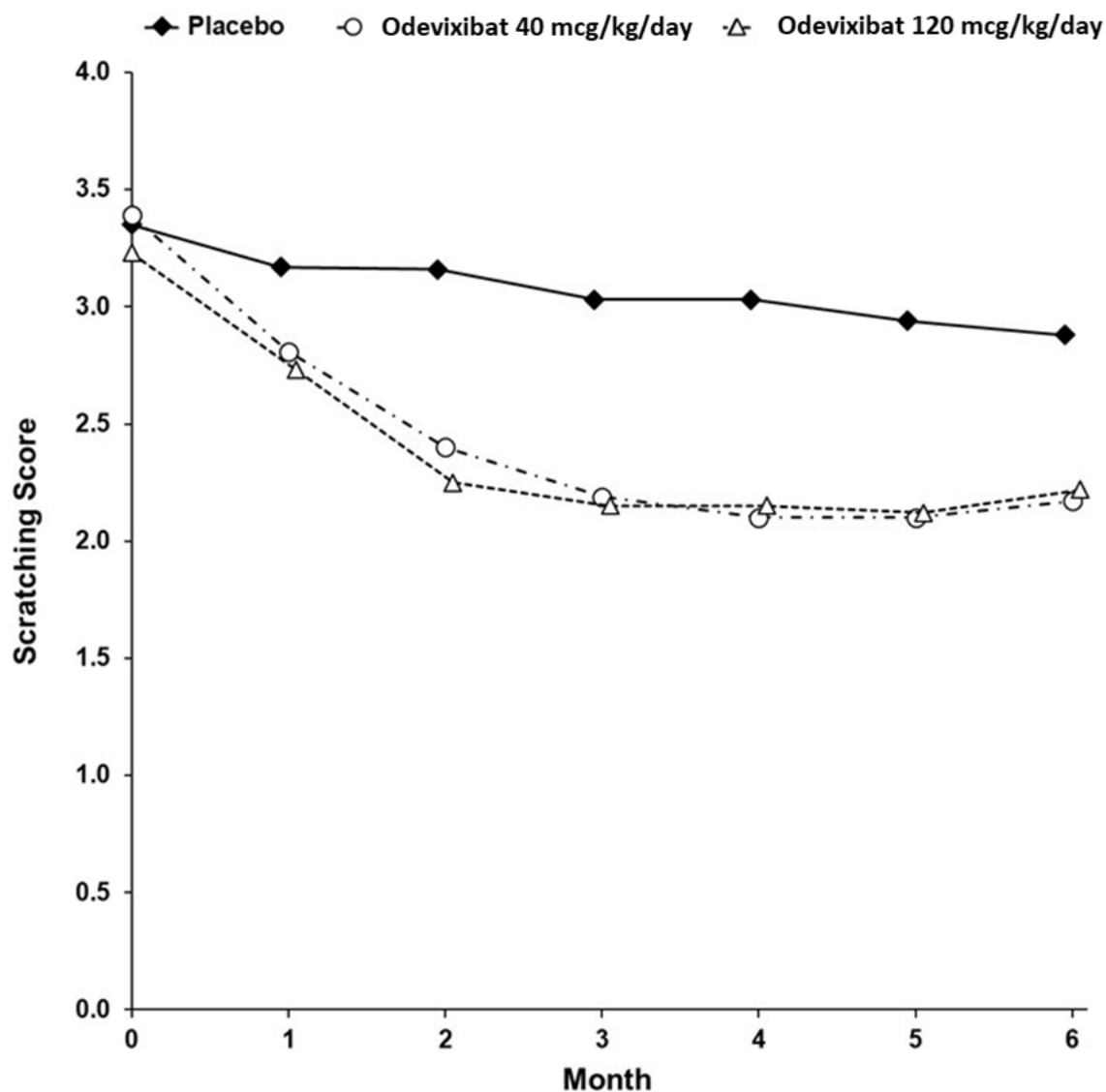
Table 4 presents the results of the comparison between BYLVAY and placebo on the mean of patients' percentage of ObsRO assessments over the 24-week treatment period that were scored as 0 (no scratching) or 1 (a little scratching). Patients treated with BYLVAY demonstrated greater improvement in pruritus compared with placebo. Figure 1 displays the mean of patients' worst weekly average scratching scores in each treatment group for each month, where the weekly average utilized the worst score from each day (morning or evening score).

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

	Placebo (n=20)	BYLVAY	
		40 mcg/kg/day (n=23)	120 mcg/kg/day (n=19)
Mean ^a Percentage of Assessments Over the Treatment Period Scored as 0 (No Scratching) or 1 (A Little Scratching) (%)			
Mean (SE)	13.2 (8.7)	35.4 (8.1)	30.1 (9.0)
Mean Difference vs Placebo (95% CI)		22.2 (4.7, 39.6)	16.9 (-2.0, 35.7)

^a Based on least squares means from analysis of covariance model with daytime and nighttime baseline pruritus scores as covariates and treatment group and stratification factors (i.e., PFIC type and age category) as fixed effects.

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



*Figure 1 presents least squares means

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Oral Pellets

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

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

Capsules

400 mcg Capsule: supplied as Size 3 capsule with medium orange opaque cap and white opaque body; imprinted “A400” (black ink). Supplied in bottles of 30 with child-resistant closure (NDC 74528-040-01).

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

Storage and Handling:

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

17 PATIENT COUNSELING INFORMATION

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

Risks

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

Administration

- **Do not mix BYLVAY with liquids.**
- Do not swallow the 200 mcg or 600 mcg capsule(s) containing Oral Pellets whole. These are intended to be opened and the contents mixed into soft food. Take BYLVAY in the morning with a meal.
- Follow stepwise administration Instructions [see *Dosage and Administration (2.2)*] for Oral Pellets and Capsules for patients unable to swallow the capsules whole.
- For patients taking bile acid binding resins, take BYLVAY at least 4 hours before or 4 hours after taking a bile acid binding resin [see *Drug Interactions (7.1)*]

Manufactured for:

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

**Instructions For Use
BYLVAY [bil-vay]
(odevixibat)
Capsules, for oral use
Oral Pellets**

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

Important information you need to know before giving or taking BYLVAY

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

Preparing to Give BYLVAY

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

Giving BYLVAY Oral Pellets:

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

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

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

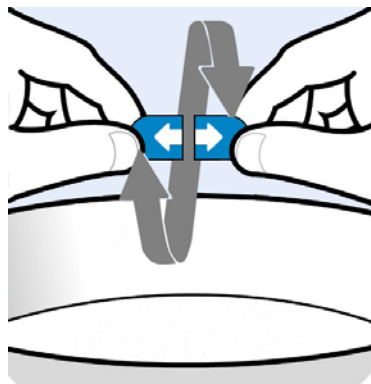


Figure A

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

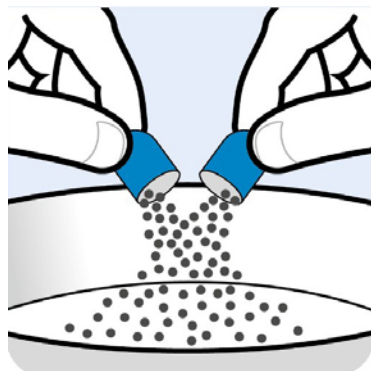


Figure B

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

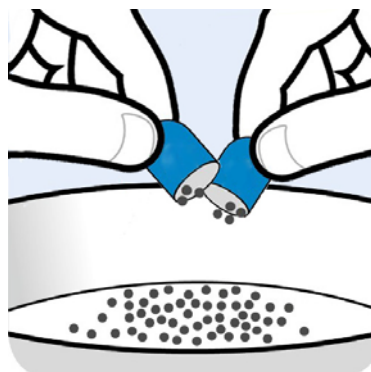


Figure C

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

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



Figure D

- Step 6.** Give the entire dose right away after mixing. **Do not** store the BYLVAY mixture for later use.
- Step 7.** Give water after the dose is taken.
- Step 8.** Dispose of (throw away) the empty Oral Pellets shell(s) in the trash.

Taking BYLVAY Capsules

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

How should I store BYLVAY Capsules or Oral Pellets?

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

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

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

What are the ingredients in BYLVAY?

Active ingredient: odevixibat.

Inactive ingredients: hypromellose and microcrystalline cellulose.

Manufactured for:

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