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 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 odevixibat 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
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). However, due to the negligible renal excretion, no dose adjustment is required for patients with mild or moderate renal impairment.

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

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 or in a liquid 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 or in a liquid.

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

Administration in soft foods
For capsules to be opened and sprinkled on soft food, 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 of all empty capsule shells.

Administration in liquids (requires use of an oral syringe)
For capsules to be opened and sprinkled in a liquid, the caregiver should be instructed to:
- hold the capsule horizontally at both ends, twist in opposite directions and pull apart to empty the pellets into a small mixing cup. The capsule should be gently tapped to ensure that all pellets will come out.
- repeat the previous step if the dose requires more than one capsule.

- add 1 teaspoon (5 mL) of an age-appropriate liquid (for example, breast milk, infant formula, or water). Let the pellets sit in the liquid for approximately 5 minutes to allow complete wetting (pellets will not dissolve).
- after 5 minutes, place the tip of the oral syringe completely into the mixing cup. Pull the plunger of the syringe up slowly to withdraw the liquid/pellet mixture into the syringe. Gently push the plunger down again to expel the liquid/pellet mixture back into the mixing cup. Repeat this 2 to 3 times to ensure complete mixing of the pellets into the liquid (pellets will not dissolve).
- withdraw the entire contents into the syringe by pulling the plunger on the end of the syringe.
- place the tip of the syringe into the front of the child's mouth between the tongue and the side of the mouth, and then gently push the plunger down to squirt the liquid/pellet mixture between the child's tongue and the side of the mouth. Do not squirt liquid/pellet in the back of the child's throat because this could cause gagging or choking.
- if any pellet/liquid mixture remains in the mixing cup, repeat the previous step until the entire dose has been administered. The mixture is not to be stored for future use.
- follow the dose with breast milk, infant formula or other age-appropriate liquid.
- dispose of all empty capsule shells.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Enterohepatic circulation
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 clinical data with odevixibat in PFIC subtypes other than 1 and 2.

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

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

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

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.

In an interaction study with a lipophilic combination oral contraceptive containing ethinyl estradiol (EE) (0.03 mg) and levonorgestrel (LVN) (0.15 mg) conducted in adult healthy females, concomitant use of odevixibat had no impact on the AUC of LVN and decreased the AUC of EE by 17%, which is not considered clinically relevant. Interaction studies with other lipophilic medicinal products have not been performed, therefore, an effect on the absorption of other fat-soluble medicinal products cannot be excluded.

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 odevixibat.

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). Odevixibat 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 odevixibat 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

Odevixibat 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 (32.2%). Other reported adverse reactions were mild to moderate increases in blood bilirubin (24.8%), ALT (14%) and AST (9.1%), vomiting (16.5%), stomach pain (11.6%), and decreases in Vitamin D (11%) and E levels (5%).

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data).

Table 3: Frequency of adverse reactions in PFIC patients

MedDRA system organ class	Frequency	Adverse drug reaction
Gastrointestinal disorders	Very common	diarrhoea[a], vomiting abdominal pain[b]
Hepatobiliary disorders	Very common	blood bilirubin increased, ALT increased
	Common	hepatomegaly, AST increased
Metabolism and nutrition ~~site~~ disorders	Very common	vitamin D deficiency
	Common	vitamin E deficiency

[a] Based on the combined frequency of diarrhoea, diarrhoea haemorrhagic and faeces soft
[b] Includes abdominal pain upper and abdominal pain lower
ALT = alanine aminotransferase
AST = aspartate aminotransferase

Description of selected adverse reactions

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

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

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

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 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 and in a Phase 2 dose-finding study (A4250-003) in paediatric patients with cholestatic liver disease, including PFIC. Study A4250-005 was a 24-week, randomised, double-blind, placebo-controlled trial conducted in 62 patients with a confirmed diagnosis of PFIC Type 1 or Type 2. Patients were randomised 1:1:1 to placebo, or 40 or 120 mcg/kg/day odevixibat and stratified by PFIC Type (1 or 2) and age (6 months

to 5 years, 6 to 12 years, and 13 to ≤ 18 years). Patients with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein and those with ALT > 10 × ULN or bilirubin > 10 × ULN were excluded. 13% of the patients had prior biliary diversion surgery. Patients completing Study A4250-005 were eligible to enrol in Study A4250-008, a 72-week open-label extension trial. In total, 116 patients were enrolled in Study A4250-008, including 37 patients who received odevixibat in Study A4250-005 and 79 patients who were treatment naïve. Results were analysed for Study A4250-005 and pooled for Studies A4250-005 and A4250-008, representing 96 weeks of treatment for patients that completed treatment with odevixibat in both trials. The primary endpoint in Studies A4250-005 and A4250-008 was the proportion of patients with at least a 70% reduction in fasting serum bile acid levels or who achieved a level ≤ 70 µmol/L at week 24.

The proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on an observer-reported outcome (ObsRO) instrument was a secondary endpoint. A positive pruritus assessment was a score of ≤ 1 or at least 1-point improvement from baseline. Pruritus assessments were conducted in the morning and evening using a 5-point scale (0-4). Additional secondary endpoints included changes from baseline to end of treatment in growth, sleep parameters (per ObsRO) and ALT.

Median (range) age of patients in Study A4250-005 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] µmol/L, respectively) and placebo-treated patients (3.0 [0.143] and 247.5 [101.1] µmol/L, respectively). Demographic and baseline characteristics of the pooled phase 3 population were generally consistent with the Study A4250-005 population. 36 (30%) of patients had PFIC Type 1, 70 (58%) had PFIC Type 2, 7 (6%) had PFIC Type 3, 4 (3%) had the episodic form of PFIC, and 2 (2%) each had PFIC Type 4 and PFIC Type 6.

Table 4 presents the results of the comparison of the key efficacy results in Study A4250-005 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 Study A4250-005

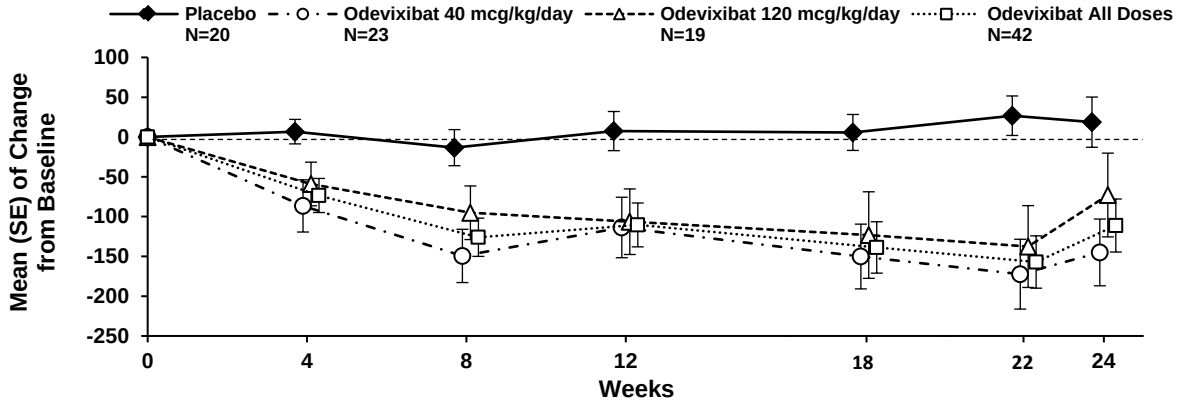
Efficacy endpoint	Placebo (N=20)	Odevixibat		
		40 mcg/kg/day (N=23)	120 mcg/kg/day (N=19)	Total (N=42)
Proportion of patients with reduction in serum bile acids at end of treatment (responders[a])				
n (%) (95% CI)	0 (0.00, 16.84)	10 (43.5) (23.19, 65.51)	4 (21.1) (6.05, 45.57)	14 (33.3) (19.57, 49.55)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

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

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

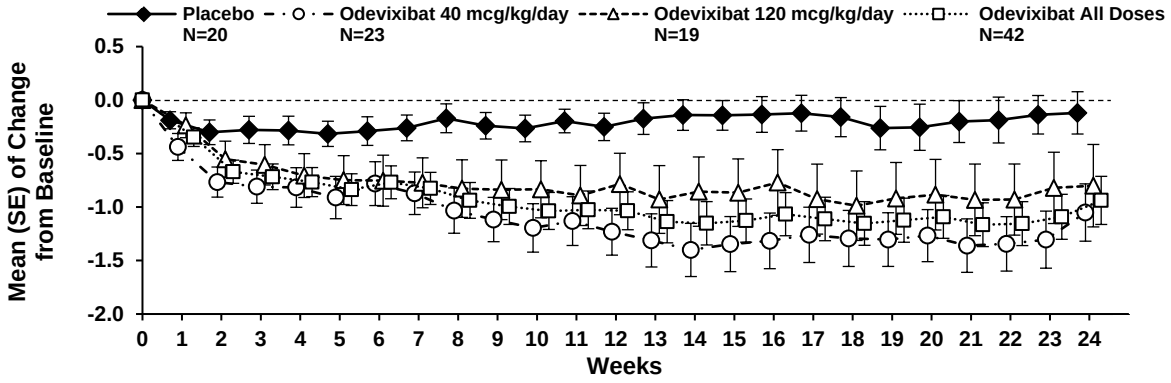
[c]Based on least squares means from an analysis of covariance model with daytime and night-time baseline pruritus scores as covariates and treatment group and stratification factors (PFIC Type and age category) as fixed effects.

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



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

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



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 Study A4250-005

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

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

In the pooled phase 3 analysis, median duration of exposure across the 121 patients having received at least one dose of odevixibat was 102.0 weeks. 87 (72%) of the 121 patients received ≥72 weeks of treatment with odevixibat.

At week 24, 36% of patients were serum bile acids responders (N=112); this effect was sustained at week 72 when 44% were serum bile acids responders (N=85). Pruritus scores improved in a consistent fashion by 63.5% at week 24 (N=102) and 72.3%, at week 72 (N=76).
The rate of serum bile acid responders at week 72 for patients with PFIC1 was 25% (7 of 28 patients), 49% (22 of 45) for PFIC2 and 67% (8 of 12) for patients with other types of PFIC. Positive pruritus assessments at the patient level over 72 weeks was similar in patients with PFIC1 (n=24) and PFIC2 (n=43), with response rates of 69% and 70%, respectively. In the subgroup of patients with other types of PFIC (PFIC3, PFIC4, PFIC6 and episodic PFIC, n=9) 91% were responders.

Mean (SD) changes from baseline at week 72 in ALT, AST, and total bilirubin in the pooled phase 3 group were -25.88 (119.18) U/L (n=78), -9.38 (69.279) U/L (N=79), and -25.65 (120.708) µmol/L (1.50 mg/dL) (n=79), respectively. Results for GGT were variable. Consistent and substantial improvement in growth was observed during longer term treatment with odevixibat. Mean height and weight z-scores improved to -1.26 and -0.75 at week 72, respectively, representing mean (SD) changes of 0.44 (0.705) (n=76) and 0.42 (0.762) (n=77), respectively.

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 × h/mL and 5.99 ng × 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 AUC_{0-24}). Reductions in maternal body weight and food consumption were noted in all dose groups (transient at the exposure multiple 1.1 of the anticipated dose).

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

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

There is insufficient information on the excretion of odevixibat in animal milk.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Hypromellose Ph.Eur

Capsule shell

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

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

Printing ink

Shellac
Propylene glycol
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 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

Ipsen Pharma
70 rue Balard
75015 Paris
France

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: 16 July 2021

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
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.	Annual interim reports are to be submitted along with the annual reassessments.

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

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/001

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

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/001

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

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/002

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

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/002

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

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/003

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

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/003

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

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/004

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

Ipsen Pharma
70 rue Balard
75015 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1566/004

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

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 enzymes might be seen in liver function tests when taking Bylvay. Before you start taking Bylvay, your doctor will measure your liver function to check how well your liver is working. Your doctor will do regular checks to monitor your liver function..

Before and during treatment, your doctor may also check your blood levels of vitamin A, D and E and your INR (international normalised ratio, which measures your risk for bleeding).

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.

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.

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 or in an age-appropriate liquid (e.g. breast milk, infant formula or water).

The larger 200 and 600 micrograms capsules are intended to be opened and sprinkled on food or in an age-appropriate liquid 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 or in an age-appropriate liquid.

Detailed instructions on how to open capsules and sprinkle on food or in a liquid can be found at the end of this package leaflet.

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:
Very common (may affect more than 1 in 10 people)
- diarrhoea, including diarrhoea with bloody stool, soft stools
- vomiting
- abdominal (belly) pain

Common (may affect up to 1 in 10 people)
- 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

Ipsen Pharma
70 rue Balard
75015 Paris
France

Manufacturer

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien/Luxembourg/ Luxemburg
Ipsen NV
België/Belgique/Belgien
Tél/Tel: +32 9 243 96 00

България
Swixx Biopharma EOOD
Тел.: +359 (0)2 4942 480

Česká republika
Ipsen Pharma s.r.o
Tel: +420 242 481 821

Danmark, Norge, Suomi/Finland, Sverige, Ísland
Institut Produits Synthèse (IPSEN) AB
Sverige/Ruotsi/Svíþjóð
Tlf/Puh/Tel/Sími: +46 8 451 60 00

Italia
Ipsen SpA
Tel: + 39 02 39 22 41

Latvija
Ipsen Pharma representative office
Tel: + 371 67622233

Lietuva
Ipsen Pharma SAS Lietuvos filialas
Tel: +370 700 33305

Magyarország
IPSEN Pharma Hungary Kft.
Tel.: + 36 1 555 5930

Deutschland, Österreich
Ipsen Pharma GmbH
Deutschland
Tel: +49 89 2620 432 89

Eesti
Centralpharma Communications OÜ
Tel: +372 60 15 540

Ελλάδα, Κύπρος, Malta
Ipsen Μονοπρόσωπη ΕΠΕ
Ελλάδα
Τηλ: +30 210 984 3324

España
Ipsen Pharma, S.A.U.
Tel: +34 936 858 100

France
Ipsen Pharma
Tél : +33 (0)1 58 33 50 00

Hrvatska
Swixx Biopharma d.o.o.
Tel: +385 1 2078 500

Ireland, United Kingdom (Northern Ireland)
Ipsen Pharmaceuticals Limited
Tel: +44 (0)1753 62 77 77

Nederland
Ipsen Farmaceutica B.V.Tel: +31 (0) 23 554 1600

Polska
Ipsen Poland Sp. z o.o.
Tel.: + 48 22 653 68 00

Portugal
Ipsen Portugal - Produtos Farmacêuticos S.A.
Tel: + 351 21 412 3550

România
Ipsen Pharma România SRL
Tel: + 40 21 231 27 20

Slovenija
Swixx Biopharma d.o.o.
Tel: + 386 1 2355 100

Slovenská republika
Ipsen Pharma, organizačná zložka
Tel: + 420 242 481 821

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.

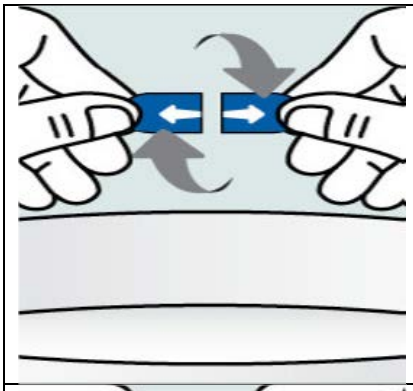
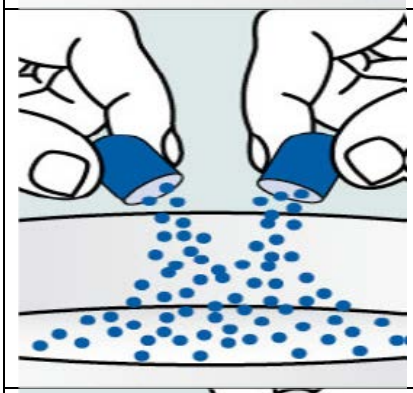
Other sources of information

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.

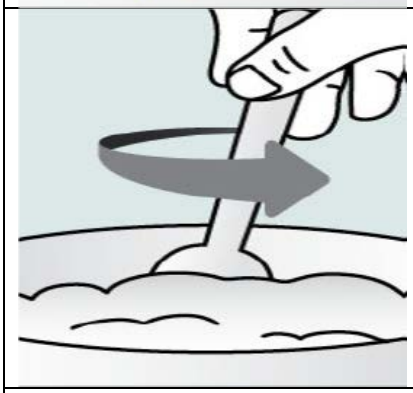
Instructions

Instructions to open capsules and sprinkle the contents on food:

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

<table>
<tr><td>  </td><td>Step 2:
• Hold the capsule horizontally at both ends, twist in opposite directions.</td></tr>
<tr><td>  </td><td>Step 3:
• Pull apart to empty the contents into the bowl of soft food.

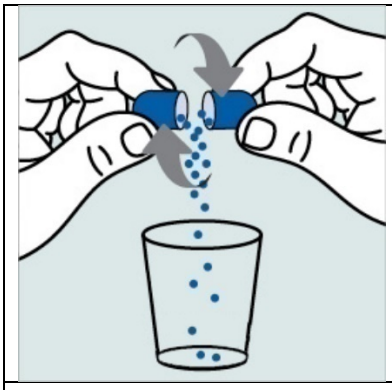
• Gently tap the capsule to ensure that all pellets come out

• Repeat the previous step if the dose requires more than one capsule.</td></tr>
<tr><td>  </td><td>Step 4:
• Gently mix the contents of the capsule into the soft food.</td></tr>
<tr><td colspan="2">• 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.</td></tr>
</table>

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

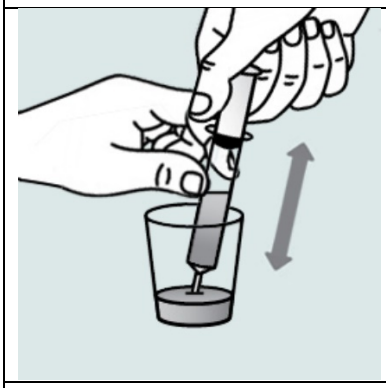
Do not administer via a bottle or “sippy cup” because the pellets will not pass through the opening. Pellets will not dissolve in liquids.

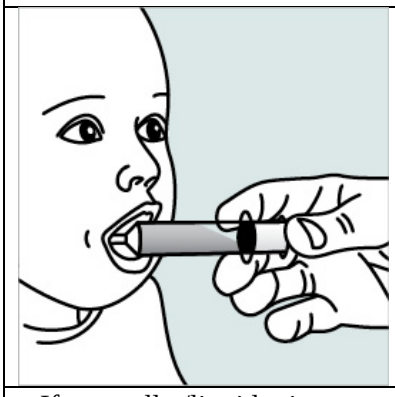
Contact your pharmacy if you do not have a suitable oral syringe for administration at home.

<table>
<tr><td>  </td><td>Step 1:
• Hold the capsule horizontally at both ends, twist in opposite directions.

• Pull apart and empty the contents into a small cup or glass.

• Gently tap the capsule to ensure that all pellets come out. Repeat this if the dose requires more than one capsule.</td></tr>
<tr><td></td><td>• Add 1 teaspoon (5 ml) of an age-appropriate liquid (e.g. breast milk, infant formula or water).

• Let the pellets sit in the liquid for approximately 5 minutes to allow complete wetting (pellets will not dissolve).</td></tr>
<tr><td>  </td><td>Step 2:
• After 5 minutes, place the tip of the oral syringe completely into the mixing cup.

• Pull the plunger of the syringe up slowly to withdraw the liquid/pellet mixture into the syringe. Gently push the plunger down again to expel the liquid/pellet mixture back into the mixing cup. Do this 2 to 3 times to ensure complete mixing of the pellets into the liquid.</td></tr>
<tr><td></td><td>Step 3:
• Withdraw the entire contents into the oral syringe by pulling the plunger on the end of the syringe.</td></tr>
<tr><td>  </td><td>Step 4:
• Place the tip of the oral syringe into the front of the child’s mouth between the tongue and the side of the mouth, and then gently push the plunger down to squirt the liquid/pellet mixture between your child's tongue and the side of the mouth. Do not squirt liquid/pellet mixture in the back of the child's throat because this could cause gagging or choking.</td></tr>
<tr><td colspan="2">• If any pellet/liquid mixture remains in the mixing cup, repeat Step 3 and Step 4 until the entire dose has been administered.
• Give the entire dose immediately after mixing. Do not store the liquid/pellet mixture for future use.</td></tr>
</table>

- Give breast milk, infant formula or other age-appropriate liquid to drink following the dose.
- Dispose of the empty capsule shells.