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

KAYFANDA 200 microgram hard capsules
KAYFANDA 400 microgram hard capsules
KAYFANDA 600 microgram hard capsules
KAYFANDA 1 200 microgram hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KAYFANDA 200 mcg hard capsules

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

KAYFANDA 400 mcg hard capsules

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

KAYFANDA 600 mcg hard capsules

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

KAYFANDA 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

KAYFANDA 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.

KAYFANDA 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.

KAYFANDA 600 mcg hard capsules

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

KAYFANDA 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

KAYFANDA is indicated for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) 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 ALGS.

Posology

The recommended dose of odevixibat is 120 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 120 mcg/kg/day dose, with a maximum daily dose of 7 200 mcg per day.

Table 1: Number of odevixibat capsules needed to achieve the nominal dose of 120 mcg/kg/day

Body weight (kg)	Total mcg dose	Number of 600 mcg capsules		Number of 1 200 mcg capsules
4 to < 7.5	600	**1**	or	Not applicable (N/A)
7.5 to < 12.5	1 200	**2**	or	1
12.5 to < 17.5	1 800	**3**	or	N/A
17.5 to < 25.5	2 400	**4**	or	2
25.5 to < 35.5	3 600	6	or	**3**
35.5 to < 45.5	4 800	8	or	**4**
45.5 to < 55.5	6 000	10	or	**5**
≥ 55.5	7 200	12	or	**6**

Capsule strength/number in **bold** is recommended based on predicted ease of administration. If necessary, any of the four capsule strengths can be combined as needed to achieve the nominal dose.

Dose reduction
Dose reduction to 40 mcg/kg/day may be considered if tolerability issues (diarrhoea that lasts ≥ 3 days, is considered severe, or requires IV hydration (see section 4.4)) occur in the absence of other causes. Once tolerability issues stabilise, the dose should be increased to 120 mcg/kg/day.

Table 2 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 2: Number of odevixibat capsules needed to achieve the nominal dose of 40 mcg/kg/day

Body weight (kg)	Total mcg dose	Number of 200 mcg capsules		Number of 400 mcg capsules
4 to < 7.5	200	**1**	or	N/A
7.5 to < 12.5	400	**2**	or	1
12.5 to < 17.5	600	**3**	or	N/A
17.5 to < 25.5	800	**4**	or	2
25.5 to < 35.5	1 200	6	or	**3**
35.5 to < 45.5	1 600	8	or	**4**
45.5 to < 55.5	2 000	10	or	**5**
≥ 55.5	2 400	12	or	**6**

Capsule strength/number in **bold** is recommended based on predicted ease of administration. If necessary, any of the four capsule strengths can be combined as needed to achieve the nominal dose.

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.

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

There are no available clinical data for the use of odevixibat in patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring haemodialysis. However, due to the negligible renal excretion, no dose adjustment is required for these patients (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).

Odevixibat has not been sufficiently studied in patients with severe hepatic impairment (Child-Pugh C). Due to minimal absorption, no dose adjustment is required. Close monitoring, however, is advised for patients with end-stage liver disease or progression to decompensation (see section 4.4).

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

Method of administration

KAYFANDA 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/caregiver 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 patient/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.

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

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and bilirubin level elevations were observed in patients receiving odevixibat (see section 4.8). Liver function tests should be monitored prior to start and during treatment with odevixibat.

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

Fat-soluble vitamins

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).

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 (CYP) 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.

Ursodeoxycholic acid (UDCA) and rifampicin

No interaction studies have been conducted with UDCA and rifampicin.

Lipophilic medicinal products

In an interaction study with a lipophilic combination oral contraceptive containing ethinyl estradiol (EE) (0.03 mg) and levonorgestrel (LVN) (0.15 mg) conducted in adult healthy females, concomitant use of odevixibat had no impact on the 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.

Paediatric population

Interaction studies have only been performed in adults. 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 in ALGS patients treated with odevixibat in clinical trials was diarrhoea(36.5%). Other reported adverse reactions were stomach pain (17.3%), mild to moderate increases in liver function tests (combined incidence of 17.3%) decreases in vitamin D (13.5%) and E levels (9.6%) and vomiting (5.8%).

Tabulated list of adverse reactions

Table 3 lists adverse reactions identified in patients with ALGS.

Adverse reactions are ranked according to system organ class and frequency grouping. Frequencies are defined 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 reported in patients with ALGS

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

[a] Includes abdominal pain upper
*See section 'Description of selected adverse reactions'.

Description of selected adverse reactions

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

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

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

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.

The maximum dose administered to healthy adult 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).

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 pharmacokinetics (PK).

Clinical efficacy

The efficacy of odevixibat in patients with ALGS was evaluated in two phase 3 trials. Study A4250-012 (ASSERT) was a 24-week, randomised, double-blind, placebo-controlled trial conducted in 52 patients with a confirmed diagnosis of ALGS. Patients were randomised 2:1 to 120 mcg/kg/day odevixibat or placebo and stratified by age at randomisation (< 10 years and ≥ 10 to < 18 years). Patients whose ALT was > 10 × upper limit of normal (ULN) or total bilirubin > 15 × ULN at screening were excluded in the ASSERT trial.

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

The primary endpoint in ASSERT was change in scratching severity score from baseline to month 6 (weeks 21 to 24) based on the worst scratching score using an observer-reported outcome (ObsRO) instrument. Scratching was assessed once in the morning and once in the evening using a 5-point scale (0-4).

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

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

Table 4 presents the results of the change from baseline in average scratching score based on the ObsRO assessments to month 6 (weeks 21 to 24) and results of the change from baseline in serum bile acids to the average of weeks 20 and 24.

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

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

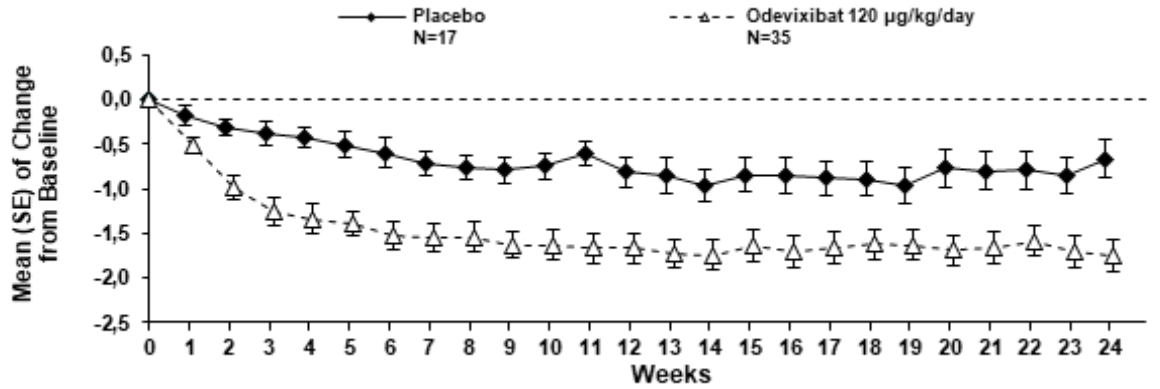
CI: confidence interval; LS Mean = Least Squares Means

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

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

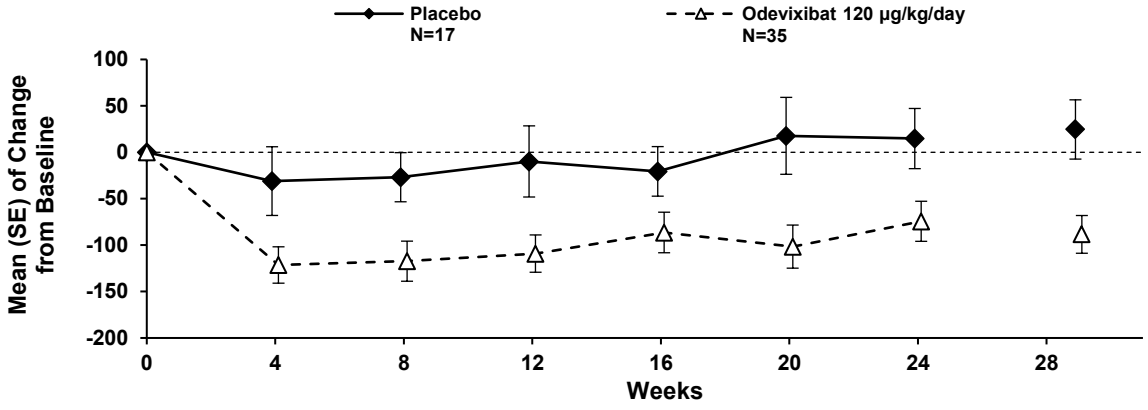
Figures 1 and 2 display graphically the mean changes standard error (SE) from baseline of patients' average scratching scores in each treatment group for each week and patients' serum bile acid levels in each treatment group for each month, respectively.

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



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

Figure 2: Mean (± SE) change from baseline in serum bile acid concentration (µmol/L) over time (ASSERT)

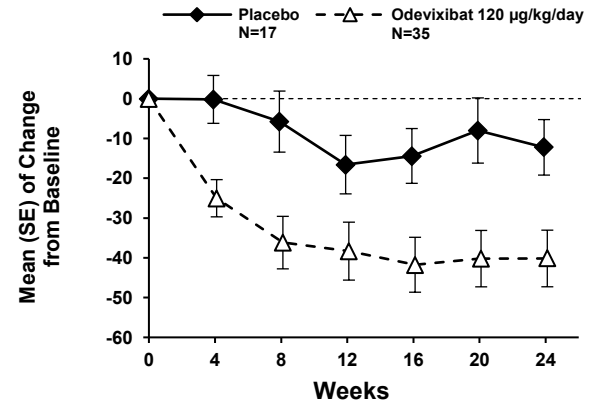


Number of Patients								
Placebo	17	16	15	16	17	15	16	17
120 µg/kg/day	35	34	35	35	35	35	33	35

Consistent with the results for improvement in pruritus (scratching) severity, odevixibat led to improvements in multiple sleep parameters. Figure 3 displays graphically the mean changes (SE) from baseline for improvement in two of the sleep parameters by treatment group for each month, including percentage of days with help falling asleep and daytime tiredness score. Similar results were observed over time for percentage of days the child required soothing to go to sleep and the percentage of days the child slept with the caregiver.

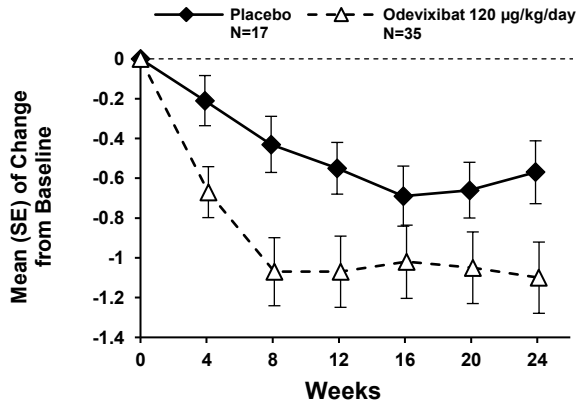
Figure 3: Mean (±SE) change from baseline in sleep parameters over time (ASSERT)

Percentage of days with help falling asleep



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

Tiredness score



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

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

Continued treatment with odevixibat 120 mcg/kg/day in ASSERT-EXT led to further improvements in pruritus score with results for the pooled population at weeks 69-72 (n = 43) showing mean (SD) changes from baseline of -1.95 (0.838). For those 31 patients who received odevixibat in both Phase 3 studies and had data available for analysis, continued improvement was observed through weeks 93-96 with mean (SD) change from baseline of -2.18 (0.876). The reduction in serum bile acid levels was maintained at week 72, when mean change from baseline was -119.4 µmol/L (-48.8 µg/mL; n = 44). Among those 30 patients who received odevixibat in both Phase 3 studies and had data available for analysis at week 96, change from baseline in serum bile acid levels was -123.9 µmol/L (-50.6 µg/mL). Improvements in sleep parameters, serum cholesterol levels and xanthomas were maintained during long-term treatment.

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. Observed exposures in paediatric patients (age between 0.756 and 17.1 years; body weight from 5.6 to 58 kg) are limited to trough values; for the 120 mcg/kg/day dose the trough values were below the limit of detection for 40% of the samples in ALGS patients. The mean C_{max} value in a paediatric ALGS patient population for the 120 mcg/kg/day dose is 1.13 ng/mL and the mean AUC value was 13.2 ng × h/mL. No accumulation of odevixibat was observed 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 / pharmacodynamic (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 volume of distribution (V/F) in ALGS patients is predicted to be 1160 L. The geometric mean body weight adjusted V/F for ALGS is 57.9 L/kg.

Biotransformation

Odevixibat is minimally metabolised in humans.

Elimination

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

Linearity/non-linearity

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

Pharmacokinetic/pharmacodynamic relationship(s)

Consistent with the mechanism and site of action of odevixibat in the gastrointestinal tract no relationship between systemic exposure and clinical effects is observed. Also, no dose-response relationship could be established for the investigated dose range 10-200 mcg/kg/day and the PD parameters 7α-hydroxy-4 cholesten-3 one (C4) and fibroblast growth factor 19 (FGF19).

Special populations

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

Hepatic impairment
All patients with ALGS presented with some degree of hepatic impairment because of the disease. Based on population PK analysis, patients with mild hepatic impairment (Child-Pugh A) exhibited comparable pharmacokinetics compared to other subjects with normal hepatic function. Patients with moderate hepatic impairment (Child-Pugh B) presented a 77.0% lower CL/F relative to patients with mild hepatic impairment or no hepatic impairment and exposure of odevixibat was 4- to 9-fold higher in patients with moderate hepatic impairment. The plasma AUC at 120 mcg/kg/day in patients with Child-Pugh A ranged from 1.52 to 10.4 ng × h/mL and in patients with Child-Pugh B was between 5.50 to 74.5 ng × h/mL. Although, CL/F values were lower and V/F values were larger in patients with Child Pugh B compared to other subjects, no accumulation of odevixibat was observed and the safety profile was comparable between the patient groups. No data are available for patients with severe hepatic impairment (Child-Pugh C).

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 not being 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 transporters (OATP1B1, OATP1B3, OAT1, OAT3), organic cation transporter (OCT2), multidrug and toxin extrusion transporters (MATE1 or MATE2-K).

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

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, 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 ≥ 1.6 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 0.5 of the anticipated dose).

Starting from the exposure multiple of 0.5 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

Capsule shell

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

KAYFANDA 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/1/24/1854/001
EU/1/24/1854/002
EU/1/24/1854/003
EU/1/24/1854/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 September 2024

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
Non-interventional Post authorisation safety study (PASS): In order to further investigate the long-term safety of odevixibat in the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older, the MAH shall conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with Alagille syndrome (ALGS) treated with odevixibat.	Annual interim reports are to be submitted along with the annual reassessments.
In order to ensure adequate monitoring of safety and efficacy of odevixibat in the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of odevixibat.	Annual (within annual reassessment)

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

KAYFANDA 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/1/24/1854/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

KAYFANDA 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

KAYFANDA 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/1/24/1854/001

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

KAYFANDA 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/1/24/1854/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

KAYFANDA 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

KAYFANDA 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/1/24/1854/002

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

KAYFANDA 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/1/24/1854/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

KAYFANDA 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

KAYFANDA 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/1/24/1854/003

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

KAYFANDA 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/1/24/1854/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

KAYFANDA 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

KAYFANDA 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/1/24/1854/004

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

KAYFANDA **200 microgram hard capsules**
KAYFANDA **400 microgram hard capsules**
KAYFANDA **600 microgram hard capsules**
KAYFANDA **1 200 microgram 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 KAYFANDA is and what it is used for

What is KAYFANDA
KAYFANDA contains the active substance odevixibat. This medicine helps with the removal of bile acids, which are found in the digestive fluid called bile, a fluid made in the liver that helps to break down fats in the intestine. After helping with digestion, bile acids are taken up from the intestine and move back into the liver.

What is KAYFANDA used for
KAYFANDA is used to treat itching caused by bile build-up in patients aged 6 months or older who have Alagille syndrome (ALGS).

ALGS is a rare genetic disease that may affect many different parts of the body, including the liver, heart, eyes, face, skeleton, blood vessels, and kidneys. Patients with this syndrome have reduced bile flow, leading to a build-up of bile acids in the blood and in the liver (cholestasis) that gets worse over time and is often accompanied with severe itching.

How does KAYFANDA (odevixibat) work
The active substance in Kayfanda, odevixibat, reduces the uptake of bile acids from the intestine. This allows them to pass out of the body in the stool and prevents their build-up in the liver. By doing this, odevixibat lowers the amount of bile acids that are present in the blood.

2. What you need to know before you take KAYFANDA

Do not take KAYFANDA

- 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 KAYFANDA if you have:
- severely reduced liver function
- reduced stomach or bowel function, or reduced flow of bile acids between liver, gallbladder and small intestine, due to medicines, surgical procedures or diseases other than ALGS. These may reduce the effect of odevixibat

Talk to your doctor if you develop diarrhoea while taking KAYFANDA. If you have diarrhoea, drink plenty of liquids to prevent dehydration.

Increased levels in liver enzymes may be seen in liver function tests during treatment with KAYFANDA. Your doctor will check your liver function prior to and during KAYFANDA treatment. Your doctor may recommend more frequent monitoring if you have elevated liver function test results.

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

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

Other medicines and KAYFANDA

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.

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.

Use of KAYFANDA is not recommended during pregnancy and in women of childbearing potential who are not using birth control.

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 odevixibat treatment, considering the benefit of breast-feeding to the baby and of odevixibat to the mother.

Driving and using machines

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

3. How to take KAYFANDA

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.

How much KAYFANDA should you take

- The dose of odevixibat is based on your weight. Your doctor will work out the right amount and strength of capsules for you to take.
- The recommended dose is 120 micrograms of odevixibat per kilogram of body weight once daily (up to a maximum daily dose of 7200 micrograms once daily). Your doctor may recommend the dose to be reduced to 40 micrograms of odevixibat per kilogram body weight once daily if you have diarrhoea that lasts ≥ 3 days, is considered severe, or requires IV hydration.

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

How to use KAYFANDA

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 microgram capsules are intended to be opened and sprinkled on food or in an age-appropriate liquid but may be swallowed whole.

The smaller 400 microgram and 1200 microgram 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 you take more KAYFANDA than you should

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

Possible overdose symptoms are diarrhoea and stomach and bowel problems.

If you forget to take KAYFANDA

If you miss taking KAYFANDA, take the forgotten dose as soon as possible, but do not take more than one dose per day.

If you stop taking KAYFANDA

Do not stop taking KAYFANDA 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
- abdominal (belly) pain

common (may affect up to 1 in 10 people)
- vomiting
- 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 KAYFANDA

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 KAYFANDA contains

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

- The other ingredients are:

  Capsule content

  Microcrystalline cellulose, hypromellose

  Capsule shell

  KAYFANDA *200 microgram and 600 microgram hard capsules*
  Hypromellose, titanium dioxide (E171), yellow iron oxide (E172)

  KAYFANDA *400 microgram and 1 200 microgram hard capsules*

Hypromellose, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172)

Printing ink

Shellac, propylene glycol, black iron oxide (E172)

What KAYFANDA looks like and contents of the pack

KAYFANDA 200 microgram hard capsules:
Size 0 capsule (21.7 mm × 7.64 mm) with ivory opaque cap and white opaque body; imprinted "A200" with black ink.

KAYFANDA 400 microgram hard capsules:
Size 3 capsule (15.9 mm × 5.82 mm) with orange opaque cap and white opaque body; imprinted "A400" with black ink.

KAYFANDA 600 microgram hard capsules:
Size 0 capsule (21.7 mm × 7.64 mm) with ivory opaque cap and body; imprinted "A600" with black ink.

KAYFANDA 1 200 microgram hard capsules:
Size 3 capsule (15.9 mm × 5.82 mm) with orange opaque cap and body; imprinted "A1200" with black ink.

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

Marketing Authorisation Holder

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Manufacturer

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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.

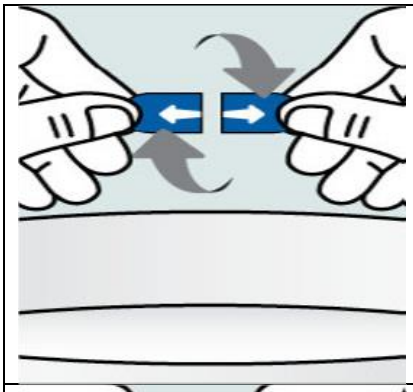
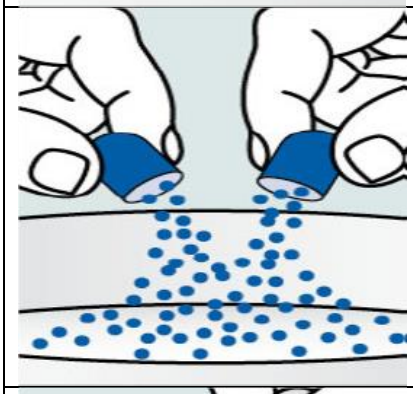
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

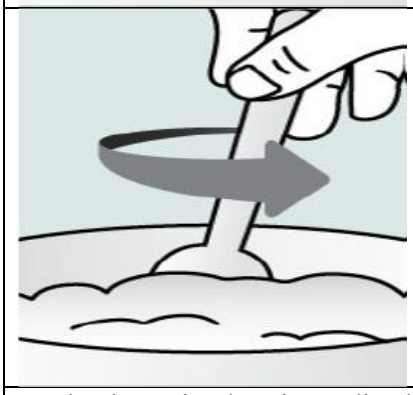
Instructions

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.

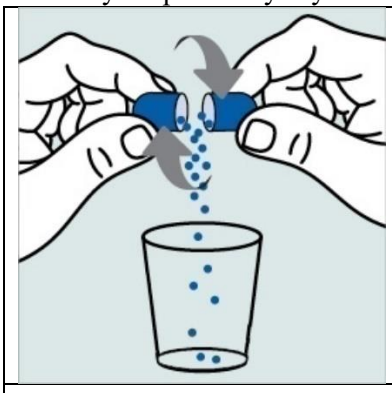
<table>
<tr><td>  </td><td>Step 2:
• Hold the capsule horizontally at both ends, twist in opposite directions.</td></tr>
<tr><td>  </td><td>Step 3:
• Pull apart to empty the contents into the bowl of soft food.

• 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>

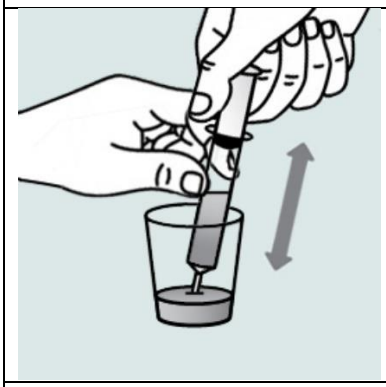
Instructions to open capsules and sprinkle the contents in an age-appropriate liquid

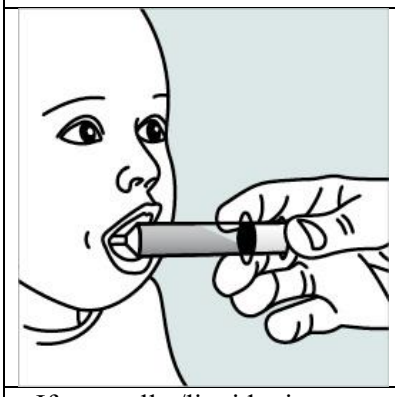
Contact your pharmacy if you do not have a suitable oral syringe for administration at home.

<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. Pellets will not pass through the opening of bottles or “sippy cups”.

• 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 in liquids).</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.
• Give breast milk, infant formula or other age-appropriate liquid to drink following the dose.
• Dispose of the empty capsule shells.</td></tr>
</table>