swissmedic

Date: 22 January 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Bylvay

International non-proprietary name:	odevixibat
Pharmaceutical form:	capsule, hard
Dosage strength(s):	200 mcg, 400 mcg, 600 mcg, 1200 mcg
Route(s) of administration:	oral
Marketing authorisation holder:	IPSEN Pharma Schweiz GmbH
Marketing authorisation no.:	69600
Decision and decision date:	approved on 4 December 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ABCB11	ATP-binding cassette, sub-family B member 11, also known as BSEP
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALGS	Alagille syndrome
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
ATP	Adenosine triphosphate
ATP8B1	ATPase phospholipid transporting 8B1
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BA	Bile acids
BSEP	Bile salt export pump, also known as ABCB11
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DSMB	Data Safety Monitoring Board
EMA	European Medicines Agency
ERA	Environmental risk assessment
EU	European Union
FDA	Food and Drug Administration (USA)
FGF19	Fibroblast growth factor 19
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IBAT	Ileal bile acid transporter
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
INR	International normalised ratio
ITT	Intention-to-treat
JAG1	Jagged canonical Notch ligand 1
LDPE	Low density polyethylene
LoQ	List of Questions
LS	Least square
LTE	Long-term extension
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
Max	Maximum
Mcg	Microgram
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NOTCH2	Neurogenic locus notch homolog protein 2

PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PEBD	Partial external biliary diversion
PFIC	Progressive familial intrahepatic cholestasis
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
sBA	Serum bile acids
SD	Standard deviation
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
US	United States

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for odevixibat in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status for both indications in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status for the indication of treatment of progressive familial intrahepatic cholestasis (PFIC) was granted on 22 December 2022.
Orphan drug status for the indication of treatment of Alagille syndrome (ALGS) was granted on 24 May 2024.

2.2 Indication and dosage

2.2.1 Requested indication

Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.
Bylvay is indicated for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older.

The applicant withdrew part of the indication initially claimed for Bylvay for the disease-modifying treatment of PFIC and the treatment of cholestatic pruritus in patients with ALGS aged between 6 and 12 months.

2.2.2 Approved indication

Bylvay is indicated for the treatment of cholestatic pruritus in patients with

- Progressive familial intrahepatic cholestasis (PFIC) aged 6 months and older
- Alagille syndrome (ALGS) aged 12 months and older.

Warnings and precautionary measures are to be taken into account (see "Warnings and Precautions" and "Clinical Efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:

- PFIC:

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

- ALGS:

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

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	27 June 2024
Formal objection	18 July 2024
Response to formal objection	12 September 2024
Formal control completed	24 September 2024
List of Questions (LoQ)	22 January 2025
Response to LoQ	17 April 2025
Preliminary decision	11 July 2025
Response to preliminary decision	4 September 2025
Labelling corrections and/or other aspects	3 November 2025
Response to labelling corrections and/or other aspects	12 November 2025
2nd round labelling corrections and/or other aspects	17 November 2025
Response to 2nd round labelling corrections and/or other aspects	24 November 2025
Final decision	4 December 2025
Decision	approval

3 Medical context

- **Progressive familial intrahepatic cholestasis (PFIC)**

PFIC is a rare group of autosomal recessive liver disorders characterised by impaired bile acid (BA) secretion and transport. It typically manifests in early childhood, leading to progressive liver damage and potential liver failure. The estimated prevalence is 1 in 50,000–100,000 live births, with equal male and female incidence. Survival rates without surgical biliary diversion or liver transplantation are poor, with only 50% surviving to age 10 and <10% to age 20.

While historically classified to 3 main types (PFIC1, PFIC2, PFIC3), ongoing genetic research has identified up to 12 distinct subtypes linked to different gene defects affecting bile secretion. PFIC1 and PFIC2 are most common. PFIC1 (ATP8B1-related) arises from mutations affecting phospholipid transport, causing not only BA retention, but also systemic symptoms like pancreatitis and hearing loss. PFIC2 (ABCB11-related) results from loss of bile salt export pump (BSEP) function, leading to severe cholestasis, rapid liver damage, and increased hepatocellular carcinoma risk. Other PFIC subtypes are (very) rare and less investigated. All subtypes share debilitating symptoms like intense pruritus and malabsorption of fat-soluble vitamins.

Diagnosis relies on molecular genetic testing: ATP8B1 mutations confirm PFIC1, and ABCB11 mutations confirm PFIC2. Treatment focuses on symptom relief (specifically pruritus), slowing disease progression, and managing complications. Therapies include ursodeoxycholic acid (UDCA), BA sequestrants, and surgical approaches like partial external biliary diversion (PEBD). Liver transplantation is often required, with curative outcomes in PFIC2 but limited effectiveness in PFIC1 due to extrahepatic manifestations.

Emerging therapies, such as ileal bile acid transporter (IBAT) inhibitors (e.g. odevixibat, maralixibat), aim to alleviate pruritus by reducing BA reabsorption via interruption of the enterohepatic BA circulation, but they may risk exacerbating cholestasis via potential induction of BA synthesis in hepatocytes.

- **Alagille syndrome (ALGS)**

ALGS is a rare autosomal dominant genetic disorder with a prevalence of 1:30,000 to 1:70,000. It is the most common inherited cause of childhood cholestasis. Mutations in the JAG1 gene (90% of cases) or NOTCH2 gene disrupt the Notch signalling pathway, causing the syndrome.

ALGS presents highly variably with chronic cholestasis, cardiovascular abnormalities, butterfly vertebrae, renal anomalies, characteristic facies, and posterior embryotoxon. Hepatic features include bile duct paucity, hepatomegaly, hypercholesterolaemia, xanthomas, cirrhosis, and risk of hepatocellular carcinoma. Jaundice and pruritus are common symptoms, with pruritus often emerging within the first year of life and significantly impairing quality of life. Cholestatic pruritus in ALGS can lead to sleep deprivation, fatigue, and mood disturbances, including suicidal ideation. In severe cases, pruritus alone may warrant liver transplantation. Prognosis varies depending on organ involvement; 75% of patients reach age 20, but up to 76% require liver transplantation before adulthood.

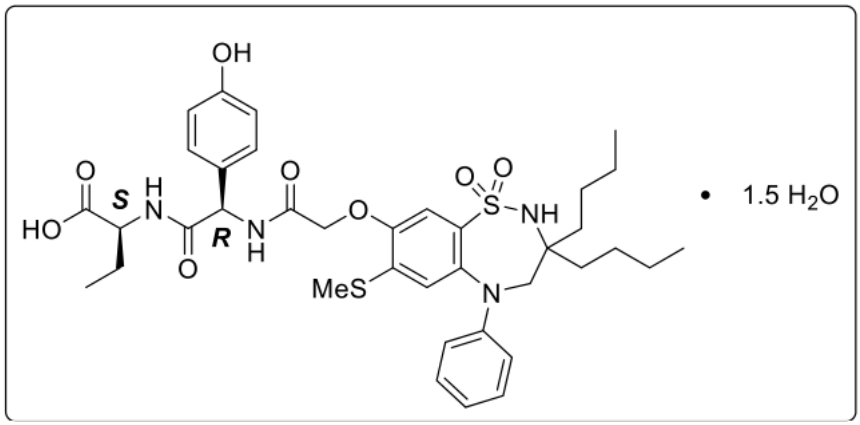
Diagnosis is based on genetic testing (JAG1 or NOTCH2 mutations) and clinical features. Treatment for cholestasis and pruritus includes UDCA, colestyramine, and rifampicin. The IBAT inhibitor maralixibat was recently approved in Switzerland for treatment of cholestatic pruritus in ALGS patients aged 3 months and older.

- **Odevixibat (Bylvay)**

Odevixibat is an orally administered, reversible, selective IBAT inhibitor targeting BA reabsorption in the distal ileum. IBAT plays a crucial role in the enterohepatic circulation, actively transporting over 95% of the circulating BA pool back to the liver. By binding locally in the gut, odevixibat reduces BA reuptake, increasing BA clearance through the gut and lowering serum BA (sBA) levels. Reducing sBA levels is proposed as an approach to treat cholestatic pruritus. The impact on intrahepatic BA levels is unclear. However, inhibiting IBAT can disrupt the fibroblast growth factor 19 (FGF19) feedback loop, potentially increasing BA synthesis in hepatocytes, exacerbating cholestasis and resulting in hepatotoxicity in some cases.

4 Quality aspects

4.1 Drug substance

INN	Odevixibat sesquihydrate
Chemical name	(2S)-2-{[(2R)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5. tetrahydro-1H-1λ^6,2,5-benzothiadiazepin-8-yl]oxy}acetamido)-2-(4-hydroxyphenyl)acetyl]amino}butanoic acid sesquihydrate
Molecular formula	C_{37} H_{48} N_4 O_8S_2 • 1.5 H_2O
Molecular mass	768.0 g/mol (sesquihydrate form)
Molecular structure	

Physicochemical properties: White to off-white solid, hygroscopic (reversible), and with pH-dependent solubility, insoluble in aqueous buffers pH 1 to 4 at 37°C and exhibiting maximum solubility at neutral pH.

Synthesis: The drug substance is obtained through a multi-stage synthetic process, involving alkylation, coupling of intermediates, hydrolysis and recrystallisation to yield odevixibat sesquihydrate.

Specification: In order to ensure a consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability: Appropriate stability data have been generated, resulting in a suitable retest period. Based on the results, a satisfactory re-test period has been established when stored below 25 °C in double Low Density Polyethylene (LDPE) bags with desiccant placed between the inner and outer LDPE bags. The double LDPE bags are placed in an aluminium can.

4.2 Drug product

Description and composition: Bylvay 200 micrograms (mcg), 400 mcg, 600 mcg and 1200 mcg are hard capsules containing coated pellets that are intended for direct oral administration either by swallowing the capsules or by sprinkling the contents of the capsules onto a food vehicle. The coated pellets are aqueous-based, film-coated and encapsulated in hypromellose hard capsules. The different strengths are uniquely identified with a combination of capsule colours and markings.

Pharmaceutical development: The initial formulation as a powder in a capsule evolved over the course of development to reach the final proposed formulation, which consists of coated pellets with active

substance in a capsule. Compatibility of the drug substance with the excipients was demonstrated, as well as the release of the product at the site of action through appropriate dissolution experiments.

Manufacture: The manufacture consists of dispersing the drug substance as a sprayable liquid form, which is then used to coat spherical inert pellets before being encapsulated in hypromellose hard capsules.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include relevant physicochemical characteristics, identification of the drug substance, assay, purity and microbiological tests.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines. The storage recommendation is “Store at 15 - 30°C. Store in the original package in order to protect from light”.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

For the review of the marketing authorisation application (MAA) for Bylvay, the Division Nonclinical Assessment at Swissmedic conducted an abridged evaluation, which was essentially based on the CHMP assessment report of the EMA dated 20 May 2021 (EMA/CHMP/150674/2021) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Bylvay in the proposed indications. The pharmaco-toxicological profile has been sufficiently characterised. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA. The available assessment report and respective product information from EMA were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology see the Information for healthcare professionals.

6.2 Dose finding and dose recommendation

The initial estimation of odevixibat efficacy and recommended dose was based on the results of the Phase 2 open-label study (A4250-003), in which odevixibat was first administered as a single dose with a 10-day follow-up period followed by a 4-week daily treatment. In total, 20 paediatric patients diagnosed with pruritus from a cholestatic liver disease, including PFIC, ALGS and biliary atresia, were enrolled. The eligible patients had to show laboratory markers of cholestasis and total sBA at least 2 times above the upper limit of normal (ULN). The study investigated 5 subsequent dose cohorts (10, 30, 60, 100, and 200 mcg/kg/day), with 4 to 6 patients in each cohort.

A reduction in sBA levels was observed in all dose groups (10 – 200 mcg/kg/day), with the highest decrease in sBA of 62.8% observed in the 60 mcg/kg/day cohort. The other cohorts, except for the lowest dose (10 mcg/kg/day), showed a similar reduction of about 50%. Dose escalation starting from 30 mcg/kg/day did not show any additional decrease in total sBA, and there was no clear dose-response relationship starting from the 30 mcg/kg/day dose.

An improvement in pruritus and sleep disturbance was observed in all dose groups, except for 10 mcg/kg/day, with the dose of 100 mcg/kg/day demonstrating the highest numerical benefit. Numerically, patients with PFIC showed a tendency for a greater response than patients with other diagnoses.

More TEAEs occurred in the highest dose cohort (200 mcg/kg/day), although there were no specific clusters to allow a conclusion about a dose relationship. Relevant limitations of this study were i) small patient numbers per cohort, and ii) unequal distribution of various diagnoses between the cohorts. Nevertheless, based on the generated data, doses in the range of 30 – 100 mcg/kg/day were considered appropriate for further investigation in PFIC and ALGS patients.

6.3 Efficacy

- **PFIC**

Odevixibat efficacy in PFIC was assessed in a single pivotal randomised, double-blind, placebo-controlled Phase 3 trial (A4250-005) comparing odevixibat 40 and 120 mcg/kg/day administered once daily for 24 weeks to placebo in paediatric patients with PFIC1 and PFIC2 (randomisation 1:1:1). The study enrolled 62 paediatric patients aged between 6 months and 18 years, and 49 (79%) patients completed the planned 24-week treatment period. An elevated sBA concentration ≥100 µmol/L and a history of significant pruritus in the 2 weeks prior to randomisation were additional eligibility criteria. Patients with severe or prolonged diarrhoea, significantly impaired liver function (Child Pugh C) and other causes than PFIC for pruritus were excluded.

There were two primary endpoints based on the region: the US endpoint was related to pruritus and the EU/Rest of the World endpoint evaluated sBA level reduction. Secondary endpoints assessed the potential disease-modifying effect of treatment with odevixibat and were based on changes in ALT and number of patients undergoing biliary diversion surgery or liver transplantation.

The study demonstrated a statistically significant benefit for both odevixibat dose groups compared to placebo on both primary endpoints. The mean proportions of positive pruritus assessments at the patient level (defined as a scratching score [range 0 to 4] of ≤1 or at least a 1-point drop from baseline)

were 58.3% and 47.7% in the odevixibat 40 and 120 mcg/kg/day groups, respectively, compared with 28.7% in the placebo group. The proportions of patients who experienced at least a 70% reduction in sBA concentration from baseline to the end of treatment or reached a level ≤70 µmol/L after 24 weeks of treatment were 43.5% and 21.1% in the odevixibat 40 and 120 mcg/kg/day dose groups, respectively. None of the patients in the placebo group met the sBA endpoint. There was no statistical difference in any primary endpoint between both treatment groups in a post hoc analysis.

Subgroup analyses with respect to the age groups, PFIC type (1 or 2), sex, baseline sBA level and hepatic impairment were consistent with those in the total study population. Patients with moderately reduced hepatic function (Child Pugh B) seemed to benefit less from the treatment with odevixibat compared to those with mild reduction (Child Pugh A).

As one of the secondary endpoints, reductions were observed in hepatic biochemical parameters after the 24-week treatment. Results over time and across individual patients were highly variable, but by Week 24 all parameters had slightly decreased on average from baseline in the odevixibat groups compared with small mean increases observed for the placebo group. None of the 62 patients underwent biliary diversion surgery or liver transplant during the study.

Participants in the pivotal A4250-005 study could roll over to the long-term extension (LTE) trial A4250-008 after completion of the 24-week treatment period or earlier due to intolerable symptoms / lack of efficacy (cohort 1). The LTE study also enrolled new patients in a separate cohort 2. This study was open-label and uncontrolled. All patients received odevixibat at the 120 mcg/kg/day dose, although this dose selection was not reasonably justified. Overall, 56 patients, including 11 patients, who discontinued the study A4250-005 prior to Week 24, rolled over to cohort 1. The effect in patients who received odevixibat in study A4250-005 and entered the LTE with already reduced sBA levels, was maintained on average for up to an additional 72 weeks while receiving 120 mcg/kg/day odevixibat. No further reduction in sBA was observed, also not in those patients who received a dose escalation from 40 to 120 mcg/kg/day. On average improvement in pruritus severity was maintained for over 72 weeks in patients with and without dose escalation. Similar to patients initially treated with odevixibat, in therapy-naïve patients (who received placebo in study A4250-005 and patients in cohort 2), a reduction in sBA levels and pruritus improvement were observed within the first 4 weeks of treatment that could be maintained over the continuous 72-week treatment. These data support the long-term efficacy of odevixibat for up to 96 weeks.

In the LTE study A2450-008, 19 (16%) of 116 patients underwent a surgical intervention, 11 of them within 72 weeks from study baseline. Overall, 3 patients underwent surgical biliary diversion, 15 patients underwent liver transplantation, and one patient had a biliary diversion followed by a liver transplantation. Some of these patients experienced a relevant reduction in their sBA levels (up to 80% decrease compared to baseline value) and pruritus scores (up to 3-point reduction from baseline), whereas others did not. The indication for a surgical intervention (e.g. intractable pruritus, disease progression etc.) was not systematically collected, and there was no placebo arm in this trial, making it difficult to draw a conclusion about a possible disease-modifying or liver-protective effect of odevixibat in PFIC.

A post-hoc analysis was conducted, as the clinical relevance of the pruritus endpoint was difficult to determine. The proportions of pruritus assessments with a scratching score of 0 (no scratching) or 1 (a little scratching) over the 24-week treatment period were 32.0% and 28.3% in the odevixibat 40 and 120 mcg/kg/day dose groups, respectively, compared to 8.9% in the placebo group.

The optimal dose regimen for a long-term treatment is uncertain. The 40 mcg/kg/day dose was not studied in the LTE trial. A dose escalation from 40 to 120 mcg/kg/day failed to produce a further reduction in sBA levels. Stepwise (e.g. 60, 80, 100 mcg/kg/day) dose escalation / reduction was also not investigated. However, in individual patients a dose escalation led to a relevant improvement in pruritus and sBA levels, while a dose reduction led to improved tolerability. Therefore, both might be considered at the physician's discretion.

Clinical benefits of the long-term reduction in sBA levels by odevixibat are unknown. sBA levels do not provide an accurate estimate of intrahepatic BA levels that are relevant for liver-related clinical outcomes, specifically for liver disease progression. The use of a specific sBA threshold as a prognostic

marker during odevixibat treatment has not yet been clearly defined and requires confirmation in dedicated prospective studies.

To confirm a disease-modifying effect of odevixibat, a reduction in liver disease progression has to be demonstrated. Reduction of pruritus as a driving factor for delaying surgical biliary diversion and liver transplantation is not sufficient to assume a disease-modifying effect in terms of preventing liver disease progression in PFIC patients. Furthermore, a PFIC patient population without pruritus was not enrolled in the submitted studies, thus any benefit for this patient subgroup is unknown. Therefore, the indication was restricted to the treatment of cholestatic pruritus.

- **ALGS**

Odevixibat efficacy in ALGS was evaluated in a single pivotal double-blind, randomised, placebo-controlled Phase 3 trial (A4250-012) comparing odevixibat 120 mcg/kg/day over 24 weeks to placebo in patients with ALGS. The study enrolled 52 paediatric patients aged between 6 months and 15.5 years at 21 centres worldwide, although the youngest patient in the odevixibat group was 1.7 years of age. An elevated sBA concentration and a history of significant pruritus prior to randomisation were additional eligibility criteria. Patients with severe or prolonged diarrhoea, significantly impaired liver function and pruritus due to reasons other than ALGS were excluded.

Study A4250-012 met its primary efficacy endpoint. The least square (LS) mean changes of scratching severity score from baseline to Weeks 21-24 were -1.69 and -0.80 in the odevixibat and placebo groups, respectively, with a statistically significantly larger reduction in scratching with odevixibat compared to placebo. The absolute change in the scratching score in the odevixibat group was clinically meaningful (>1.5 points), as determined in the psychometric analysis. Results of the sensitivity and tipping-point analyses for the primary efficacy endpoint were consistent with the main analysis. A separate responder analysis, defined as the proportion of patients achieving at least a 1.5-point decrease in scratching score from baseline to Weeks 21-24, was statistically significant at the nominal 5% level for odevixibat compared to placebo. There was a significantly higher responder rate in the odevixibat group (54.3%) compared to the placebo group (17.6%).

The key secondary efficacy endpoint was also met. The LS mean changes from baseline to Weeks 20-24 in sBA levels were -90.35 and 22.39 µmol/L in the odevixibat and placebo groups, respectively, and the LS mean difference (95% CI) of -112.74 (-178.78, -46.69) µmol/L between the groups was statistically significant in favour of odevixibat (one-sided p = 0.0006). However, as the expected reduction in sBA levels was not pre-defined, it is difficult to make a conclusion about its clinical relevance, as the sBA levels ranged from 26 – 377 µmol/L after 24 weeks of treatment, remaining far above the ULN (10 µmol/L) in the majority of patients.

Participants in the pivotal A4250-012 study could roll over to the LTE open-label trial A4250-015 after completion of the 24-week treatment period, where all patients received odevixibat 120 mcg/kg/day. At the time of the data cut-off (Feb. 2024), 50 patients out of 52 planned were enrolled, with 44 (88.0%) patients completing the 72-week treatment period. Patients on odevixibat who completed the pivotal study entered the LTE with an already improved pruritus score and reduced sBA levels that on average remained stable with odevixibat for up to an additional 72 weeks. These data support the long-term efficacy of odevixibat for up to 96 weeks (n=30). In patients, who received placebo in the study A4250-012, a reduction in sBA and pruritus improvement were observed within the first 4 weeks of treatment that was maintained on average during continuous treatment for up to 72 weeks.

Since a positive effect on liver function tests was not observed in ALGS patients treated with odevixibat, a clinical benefit of the long-term reduction in sBA levels in ALGS patients on liver function is uncertain. No liver transplantations were reported in the pivotal trial. In the LTE only one patient who switched from placebo to odevixibat discontinued treatment, after 3.5 months, due to fulfilment of the drug-induced liver injury (DILI) criteria and underwent liver transplantation 5 days later.

Overall, 8 ALGS patients between 12 and 24 months of age were treated with odevixibat in the submitted trials, and a clinically meaningful pruritus reduction was documented in 4 of these patients after 24 weeks of treatment.

The optimal dose for ALGS patients is uncertain as no parallel arm with a lower odevixibat dose was included in the pivotal trial like it was done for the PFIC indication.

6.4 Safety

- **PFIC**

The PFIC safety database includes data from patients treated in the pivotal study A4250-005 and its open-label extension study A4250-008 (cut-off date Feb. 2024). The safety data were assessed separately and as a pool. In the Pooled Phase 3 group, the median duration of exposure was 102.0 weeks (range 4 to 272 weeks). Overall, 100 (83%) of the 121 patients had received ≥ 52 weeks, 87 (72%) had received ≥ 72 weeks, and 64 (53%) had received ≥ 96 weeks of treatment with odevixibat. The total exposure was 274.5 patient-years.

In the study A4250-005, the overall incidence of TEAEs was similar across the treatment groups (about 85%). The most common TEAEs in the odevixibat group were diarrhoea, pyrexia, upper respiratory tract infection, vomiting, ALT increased, and blood bilirubin increased. The incidence of commonly reported events was similar in the odevixibat 40 and120 mcg/kg/day dose groups, except for diarrhoea, which occurred more frequently in the 40 mcg/kg/day group. Separately collected treatment-emergent liver-related events were observed more often in the 120 mcg/kg/day dose group (32%), compared to the 40 mcg/kg/day group (22%) and placebo (20%). Most TEAEs were mild to moderate in intensity and assessed as unrelated to study treatment.

The incidence of drug-related TEAEs was higher in both odevixibat groups (about 30%) compared to placebo (15%). Treatment interruptions due to TEAEs were more commonly reported among patients who received 120 mcg/kg/day (32%) compared with patients who received 40 mcg/kg/day (13%) or placebo (5%). Treatment-emergent SAEs were reported in 3 (7%) of the 42 patients who received odevixibat and in 5 (25%) of the 20 patients who received placebo.

The events of special interest included diarrhoea, new or worsening fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation, and hepatic events. There was 1 case of clinically significant diarrhoea in each treatment group, which was considered unrelated to the study drug, and no fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation was reported. Data from 24 patients underwent review and adjudication by the Data Safety Monitoring Board (DSMB) during the study, including 18 (43%) patients who received odevixibat and 6 (30%) patients who received placebo. The incidences were 39% and 47% in the 40 and 120 mcg/kg/day groups, respectively. All 24 patients met the laboratory criteria for suspected DILI but were adjudicated by DSMB as due to the patient's underlying disease or due to other cause (e.g. acute gastroenteritis).

The TEAEs reported in the LTE study A4250-008 confirmed the safety profile observed in the pivotal study. The most common drug-related TEAEs were laboratory abnormalities, including reports of increases in total bilirubin, ALT, AST, hepatic enzymes, INR, blood creatine phosphokinase, GGT, and a decrease in vitamin D.

The highest uncertainty of odevixibat treatment relates to the possible hepatotoxicity. More liver function test elevations were observed under odevixibat treatment compared to placebo, with possible dose relationship, although hepatic laboratory value fluctuations are common in PFIC patients. While there is no superiority of the 120 mcg/kg/day dose with respect to efficacy, but numerically there are more safety events, especially associated with potential hepatotoxicity, it is reasonable to recommend the 40 mcg/kg/day dose at treatment initiation. However, the clinical impact of continuous 40 mcg/kg/day dose administration is uncertain as it was not tested for longer than 24 weeks.

- **ALGS**

The ALGS safety database includes data from 52 patients treated in the pivotal study A4250-012 and its open-label extension study A4250-015 (cut-off date Feb. 2024). The safety data were assessed separately and as a pool. In the Pooled Phase 3 group, median duration of treatment was 99.8 weeks and ranged from 15.7 to 131.3 weeks. Overall, 45 (87%) patients received odevixibat for > 72 weeks and 32 (62%) received odevixibat for > 96 weeks. The total exposure to odevixibat was 92.3 patient-years.

In the pivotal study, the proportion of patients who experienced at least 1 TEAE was similar among the arms (about 70%). The most common TEAEs (≥ 10%) among patients who received odevixibat were diarrhoea, pyrexia, COVID-19, and abdominal pain.

The incidence of drug-related TEAEs was slightly higher in the odevixibat group 22.9% (8 patients) compared to the placebo group 17.6% (3 patients), mainly driven by gastrointestinal events (diarrhoea, vomiting). Although diarrhoea is a known adverse reaction of IBAT inhibitors, while on treatment with odevixibat it was rarely severe or prolonged.

Treatment-emergent SAEs were reported at similar incidences in both groups. One patient in the odevixibat group had SAEs of haematemesis and increased INR that were assessed as related to the study drug.

No patients discontinued treatment due to a TEAE. Interruptions and dose reduction due to TEAEs were reported only in the odevixibat group.

Reduction of fat-soluble vitamin levels, specifically vitamins D and E, as well as INR increase were observed more often in the patients treated with odevixibat compared to placebo, although most of these changes were not reported as TEAEs by investigators.

Overall, 4 (11.4%) patients in the odevixibat group experienced liver-related TEAEs with a similar incidence reported in the placebo group (11.8%). However, transaminase levels showed larger increases for the odevixibat group compared to placebo, although the variability among individual patients was very high. Review of the changes over time by visit indicated that ALT and AST levels increased by Week 4 of the odevixibat treatment with mean (SD) changes of 67.2 (66.91) U/L and 51.8 (64.59) U/L, respectively, and remained on a plateau through Week 24. This ALT/AST change pattern was also observed in the LTE study in patients who switched from placebo to odevixibat treatment. In contrast to PFIC patients, in whom the ALT/AST increase after odevixibat treatment was rather transient, in ALGS patients, who continued on odevixibat in the LTE study, a further small increase in mean ALT/AST values was observed up to 96 weeks of total exposure. Thus, a potential hepatotoxicity of odevixibat, perhaps only in a certain ALGS subpopulation, cannot be ruled out.

The safety data for ALGS patients generated in the LTE up to the cut-off date generally supported the safety profile established in the pivotal trial, although the total exposure to odevixibat was still limited.

6.5 Final clinical benefit risk assessment

PFIC and ALGS are rare, heterogeneous genetic disorders in which cholestatic pruritus represents the most common and most debilitating symptom with limited treatment options. The efficacy of odevixibat in reducing pruritus severity has been demonstrated in both patient populations, PFIC and ALGS. The safety profile was considered acceptable, with no prohibitive safety signals identified, but potential hepatotoxicity and deficiencies of fat-soluble vitamins require active monitoring.

Overall, the benefit-risk balance for the treatment of cholestatic pruritus with odevixibat at a dose of 40 mcg/kg/day in patients with PFIC aged at least 6 months, and at a dose of 120 mcg/kg/day in patients with ALGS aged 12 months and older, is considered positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Bylvay was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼This medicinal product is subject to additional monitoring. This enables a fast identification of new findings regarding safety. Healthcare professionals are asked to report any suspected new or serious adverse reactions. Refer to section „Undesirable effects“ for how to report adverse reactions.

Bylvay®

Composition

Active substance

Odevixibat (as odevixibat sesquihydrate).

Excipients

Capsule content :
Microcrystalline cellulose, Hypromellose.

Capsule shell :
Bylvay 200 mcg and 600 mcg hard capsules:
Hypromellose, Titanium dioxide, Yellow iron oxide.

Bylvay 400 mcg and 1200 mcg hard capsules:
Hypromellose, Titanium dioxide, Yellow iron oxide, Red iron oxide.

Printing ink:
Shellac, Propylene glycol, Black iron oxide

Pharmaceutical form and active substance per 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.
Each hard capsule contains odevixibat sesquihydrate equivalent to 200 micrograms odevixibat.

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

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.

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

Bylvay 1200 mcg hard capsules

Size 3 capsule (15.9 mm × 5.82 mm) with orange opaque cap and body; imprinted “A1200” with black ink.
Each hard capsule contains odevixibat sesquihydrate equivalent to 1200 micrograms odevixibat.

Therapeutic indications

Bylvay is indicated for the treatment of cholestatic pruritus in patients with

- Progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months and older
- Alagille syndrome (ALGS) in patients aged 12 months and older.

Warnings and precautionary measures are to be taken into account (see “Warnings and Precautions” and “Clinical Efficacy”).

Posolgy and method of administration

Posology for PFIC
Treatment must be initiated and supervised by physicians experienced in the management of PFIC.
The recommended dose of Bylvay is 40 mcg/kg administered orally once daily in the morning.
Dose escalation
If an adequate clinical response (improvement in pruritus and reduction of serum bile acid levels) has not been achieved after 3 months of continuous therapy, the dose may be increased to 120 mcg/kg/day, where the maximum daily dose of 7200 mcg cannot be exceeded (see “warnings and precautions for use”). Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with Bylvay.

Posology for ALGS
Treatment must be initiated and supervised by physicians experienced in the management of ALGS.
The recommended dose of Bylvay for treatment in ALGS is 120 mcg/kg administered orally once daily in the morning. Alternative treatment should be considered in patients for whom no treatment benefit can be established following 6 months of continuous daily treatment with Bylvay.
Dose reduction
In patients with ALGS, dose reduction to 40 mcg/kg/day may be considered if tolerability issues occur in the absence of other causes. Once tolerability issues stabilize, increase to 120 mcg/kg/day.

All available capsule strengths are interchangeable and may be swallowed whole or opened and sprinkled. The strength chosen to support total daily dose should be based on predicted ease of

administration for each patient, i.e., total number of capsules, size of capsules, ability to swallow whole capsules.
Table 1 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.

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 7200 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 1200 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.

Missed doses

If a dose of Bylvay is missed, the patient should take the forgotten dose within 12 hours of the time it is usually taken, and the original dosing should be resumed. . If more than 12 hours have elapsed since the missed dose, that dose can be skipped and the original dosing schedule resumed.

Special dosage instructions

Patients with renal impairment

There are no available clinical data for the use of Bylvay in patients with moderate or severe renal impairment or end-stage renal disease (ESRD) requiring haemodialysis (see “Pharmacokinetics”). However, due to the minimal plasma concentrations and negligible renal excretion, no dose adjustment is required for patients with renal impairment.

Patients with hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (see “Pharmacokinetics”).
Bylvay has not been studied in patients with severe hepatic impairment (Child Pugh C). Permanently discontinue Bylvay if signs of hepatic decompensation occur (e.g.variceal haemorrhage, ascites, hepatic encephalopathy; see “Contraindications” and “Warnings and precautions for use”).

Elderly
For patients 65 years of age and older no clinical data are available.

Paediatric population

Bylvay is not approved for use in PFIC patients less than 6 months of age and ALGS patients less than 12 months of age.

Method of administration

Bylvay is taken per os. To be taken with or without food in the morning.

The larger 200 mcg and 600 mcg capsules are intended to be opened and sprinkled on soft food or in a liquid but may be swallowed whole.
The smaller 400 mcg and 1200 mcg capsules are intended to be swallowed whole but may be opened and sprinkled on soft food or in a liquid.
If the capsule is to be swallowed whole, the patient should be instructed to take it with a glass of water in the morning.

Administration in soft foods:
For capsules to be opened and sprinkled on food with a soft consistency, the patient or the supervisor should be instructed to:

1. Place a small quantity (up to 30 mL/2 tablespoons) of soft food (yoghurt, apple sauce, oatmeal porridge, banana puree, carrot puree, chocolate-flavoured pudding or rice pudding) in a bowl. The food should be at or below room temperature.

2. Hold the capsule horizontally at both ends, twist in opposite directions and pull apart to empty the pellets into the bowl of soft food. The capsule should be gently tapped to ensure that all pellets will come out.
3. Repeat Step 2 if the dose requires more than one capsule.
4. Gently mix the pellets with a spoon into the food with soft consistency.
5. Administer the entire dose immediately after mixing. Do not store the mixture for future use.
6. Drink a glass of water following the dose.
7. Dispose of all empty capsule shells.

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

Pellets will not dissolve in liquids.
For capsules to be opened and sprinkled in a liquid, the patient or the supervisor should be instructed to:

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

Contraindications

Prior or active signs of hepatic decompensation (e.g. variceal haemorrhage, ascites, hepatic encephalopathy; see “Warnings and precautions for use”).
Hypersensitivity to the active substance or to any of the excipients listed according composition.

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 Bylvay. 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 Bylvay in PFIC subtypes other than 1 and 2. In patients with PFIC5, the efficacy of odevixibat has not been studied.
Hepatotoxicity
Bylvay treatment is associated with a potential for drug-induced liver injury (DILI). In the PFIC and ALGS trials, treatment-emergent elevations of liver tests or worsening of liver tests occurred. Of the six patients who experienced potential DILI, two underwent liver transplant. Assessment of liver function tests and the establishment of a personal baseline is recommended for patients prior to initiating Bylvay, with monitoring per standard clinical practice. For patients with liver function test elevations more frequent monitoring is to be considered. If liver test abnormalities or signs of clinical hepatitis occur in the absence of other causes, consider dose reduction or treatment interruption. Once hepatic impairment returns to baseline, re-administration of Bylvay at the recommended dose may be considered..
Bylvay should be permanently discontinued if a patient experiences:

- persistent or recurrent liver test abnormalities, or
- signs and symptoms consistent with a clinical hepatitis upon re-administration, or
- a hepatic decompensation.

The safety and efficacy of Bylvay in patients with decompensated cirrhosis have not been established. Patients with compensated cirrhosis or portal hypertension should be monitored more frequently and treatment with Bylvay should be discontinued if hepatic decompensation occurs. IBAT inhibitors, including Bylvay, are contraindicated in patients with prior or active signs of hepatic decompensation.

Diarrhoea

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

Fat-soluble vitamin deficiency

In clinical trials, decreased levels of fat soluble vitamins were observed in some patients receiving Bylvay. Assessment of fat-soluble vitamin (FSV) levels (Vitamins A, D, E) and international normalised ratio (INR) are recommended for all patients prior to initiating Bylvay, with monitoring per standard clinical practice. If FSV deficiency is diagnosed, supplemental therapy should be prescribed. If complications of FSV deficiency occur (e.g. bleeding, fractures, etc.), consider interrupting Bylvay treatment and reassess to ensure adequate supplementation with FSV. Consider restarting Bylvay treatment once the patient is clinically stable. If FSV deficiency persists or worsens despite adequate FSV supplementation, consider permanent discontinuation of Bylvay treatment.

Lipophilic medicinal products

The absorption of lipophilic medicinal products may be affected by concomitant use of Bylvay (see section “Interactions”).

Interactions

Effect of other agents on the pharmacokinetics of odevixibat

Transporter-mediated interactions

Odevixibat is a substrate for the efflux transporter P-glycoprotein (P-gp) but not of BCRP. 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.*

Effect of odevixibat on the pharmacokinetics of other agents

Cytochrome-P450-mediated interactions

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

Preganancy, lactation

Women of childbearing potential
Women of childbearing potential should use an effective method of contraception when treated with Bylvay.
Pregnancy
There are no data from the use of Bylvay in pregnant women. Animal studies have shown reproductive toxicity (see “Preclinical Data”). Bylvay is not recommended during pregnancy and in women of childbearing potential not using contraception.
Breast-feeding
It is unknown whether odevixibat or its metabolites are excreted in human milk. There is insufficient information on the excretion of odevixibat in animal milk (see “Preclinical Data”).
A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bylvay therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.
Fertility
No fertility data are available in humans. Animal studies do not indicate any direct or indirect effects on fertility or reproduction (see “Preclinical Data”).

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile
The most commonly reported adverse reaction in the clinical development program was diarrhoea reported in 31% of patients with PFIC and 37% of patients with ALGS.
Other reported adverse reactions were vomiting and stomach pain, increases in liver function tests, hepatomegaly and decreases in vitamin D and E levels..

Tabulated list of adverse reactions

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

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) and adverse reactions identified in clinical trials in patients with ALGS from 1 to 16 years of age (median 5,7 years).

Table 3: Frequency of adverse reactions in PFIC and ALGS patients

MedDRA-system organ class **Frequency**	PFIC	ALGS
Gastrointestinal disorders		
• Very common	diarrhoea[a] (31%) vomiting (17%) abdominal pain[b] (11%)	diarrhoea[a](37%) abdominal pain[b](17%)
• Common	-	vomiting
Hepatobiliary disorders		
• Very common	blood bilirubin increased (25%) ALT increased (14%)	-
• Common	hepatomegaly AST increased	blood bilirubin increased ALT increased AST increased GGT increased hepatomegaly
Metabolism and nutrition site disorders		
• Very common	vitamin D deficiency (11%)	vitamin D deficiency (14%)
• Common	vitamin E deficiency	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
GGT= gamma glutamyl transferase

Description of selected adverse reactions

Gastrointestinal disorders adverse reactions

PFIC

In clinical trials, diarrhoea was the most common gastrointestinal adverse drug reaction reported in around 31% of patients treated with Bylvay. Most events of diarrhoea were of short duration (≤ 5 days), of mild to moderate intensity (99%) and non-serious. Dose reduction (3%), treatment interruption (7%) and discontinuation (3%) due to diarrhoea was reported with few patients requiring intravenous or oral hydration due to diarrhoea (see “warnings and precautions”).

Other commonly reported gastrointestinal disorders were vomiting (17%) and abdominal pain (11%) (including abdominal pain upper and lower), all nonserious, mild to moderate and in general not dose limiting.

ALGS

Most frequently reported adverse reaction was diarrhoea, reported in 37% of Bylvay treated patients. All events were mild to moderate in severity and non-serious. Few patients (4%) required treatment interruption and rehydration due to diarrhoea (see “warnings and precautions”). Other gastrointestinal adverse reactions were reports of abdominal pain (17%) and vomiting (6%), mild to moderate in severity and of limited duration.

Hepatobiliary disorders

PFIC

The most common hepatic adverse reactions were increases in blood bilirubin (25%), alanine aminotransferase (ALT) (14%) and aspartate aminotransferase (AST) (9%). Majority of these were mild to moderate in severity; five patients (4%) reported severe elevations in liver function tests. Treatment interruption due to increases in liver function tests have been seen in patients with PFIC treated with Bylvay. Bylvay treatment is associated with a potential for drug-induced liver injury (DILI), however most excursions in ALT, AST, and bilirubin values were also considered related to the underlying disease, as well as to intermittent concomitant viral or infectious illness, which are common at the age of the patients. Hence, monitoring of liver function tests is recommended (see “warnings and precautions”).

ALGS

The most common hepatic adverse reactions were increases in alanine aminotransferase (6%), aspartate aminotransferase ,gamma-glutamyl transferase (ALT, AST and GGT) and blood bilirubin (4% each). Most of these excursions were mild or moderate and non-serious. Bylvay treatment is associated with a potential for drug-induced liver injury (DILI). Most 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 “warnings and precautions”).

Metabolism and nutrition disorders

PFIC & ALGS

Due to the decreased release of bile acids into the intestine and risk of malabsorption, paediatric patients with PFIC and ALGS with chronic cholestasis are at risk of fat-soluble vitamin deficiencies even with supplementation (see “warnings and precautions”). Reductions in vitamin levels were observed during long-term treatment with Bylvay; the majority of these patients responded to appropriate vitamin supplementation. Overall, few patients had fat-soluble vitamin deficiencies that were refractory to supplementation (8% of ALGS and 3% of PFIC patients). These events were mild in intensity and did not lead to treatment interruption or discontinuation of Bylvay.

Post-marketing experience

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

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 Online-Portal ElViS (Electronic Vigilance System). Information can be found via www.swissmedic.ch.

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 Bylvay 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.

Properties/effects

ATC-Code

A05AX05

Mechanism of action

Odevixibat is a reversible, 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

PFIC

The efficacy of Bylvay in patients with PFIC was evaluated in one phase 3 trial (Study A4250-005). PFIC Trial 1 was a 24-week, randomised, double-blind, placebo-controlled trial conducted in 62 patients with a confirmed diagnosis of PFIC Type 1 or Type 2 and a history of significant pruritus and

presence of pruritus at baseline. Patients were randomised 1:1:1 to placebo, or 40 or 120 mcg/kg/day Bylvay 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. The primary endpoint in PFIC Trial 1 was the proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on an observer-reported outcome (ObsRO) instrument. With ObsRO the severity of scratching was assessed using a 5-point scale (0-4), from 0 (no scratching) to 4 (the most severe scratching). 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. An additional primary endpoint was the proportion of patients with at least a 70% reduction in fasting serum bile acid levels after 24 weeks of treatment or who achieved a level ≤ 70 µmol/L.

Median (range) age of patients in PFIC Trial 1 was 3.2 (0.5 to 15.9) years; 50% were male and 84% were white. 27% of patients had PFIC Type 1 and 73% had PFIC Type 2. At baseline, 81% of patients were treated with UDCA, 66% with rifampicin, and 89% with UDCA and/or rifampicin. Baseline hepatic impairment per Child-Pugh classification was mild in 66% and moderate in 34% of patients. Baseline mean (SD) eGFR was 164 (30.6) mL/min/1.73 m². Baseline mean (SD) ALT, AST and bilirubin levels were 99 (116.8) U/L, 101 (69.8) U/L, and 3.2 (3.57) mg/dL, respectively. Baseline mean (SD) pruritus score (range: 0-4) and serum bile acids levels were similar in odevixibat-treated patients (2.9 [0.089] and 252.1 [103.0] µmol/L, respectively) and placebo-treated patients (3.0 [0.143] and 247.5 [101.1] µmol/L, respectively).

Table 4 presents the results of the comparison of the key efficacy results in PFIC Trial 1 between odevixibat and placebo. Data for pruritus and serum bile acids are displayed graphically over the 24-week treatment period in Figure 1 (proportion of pruritus assessments with scores of 0 or 1) and Figure 2 (mean change from baseline in serum bile acids).

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

Efficacy endpoint	**Placebo**	**Odevixibat**	
	(N=20)	**40 mcg/kg/day (N = 23)**	**120 mcg/kg/day (N = 19)**
Proportion of positive pruritus assessments over the treatment period			
Proportion	28,74	58,31	47,69
Difference in proportion (SE) vs. placebo (95%-CI)[a]		28,23 (9,18) (9,83; 46,64)	21,71 (9,89) (1,87; 41,54)

One-sided p-value[c]		0.0019	0.0163
Proportion of patients with reduction in serum bile acids at end of treatment (responders[b])			
n (%)	0	10 (43,5)	4 (21,1)
(95%-CI)	(0,00, 16,84)	(23,19; 65,51)	(6,05; 45,57)
Difference in proportion vs. placebo (95%-CI)		0,44 (0,22; 0,66)	0,21 (0,02; 0,46)
One-sided p-value[c]		0,0015	0,0174

[a] 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.

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

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

Figure 1: Proportion of Pruritus Assessments at the Patient Level with Scores of 0 or 1 over the 24-Week Treatment Period by 4-Week Intervals – ObsRO Instrument

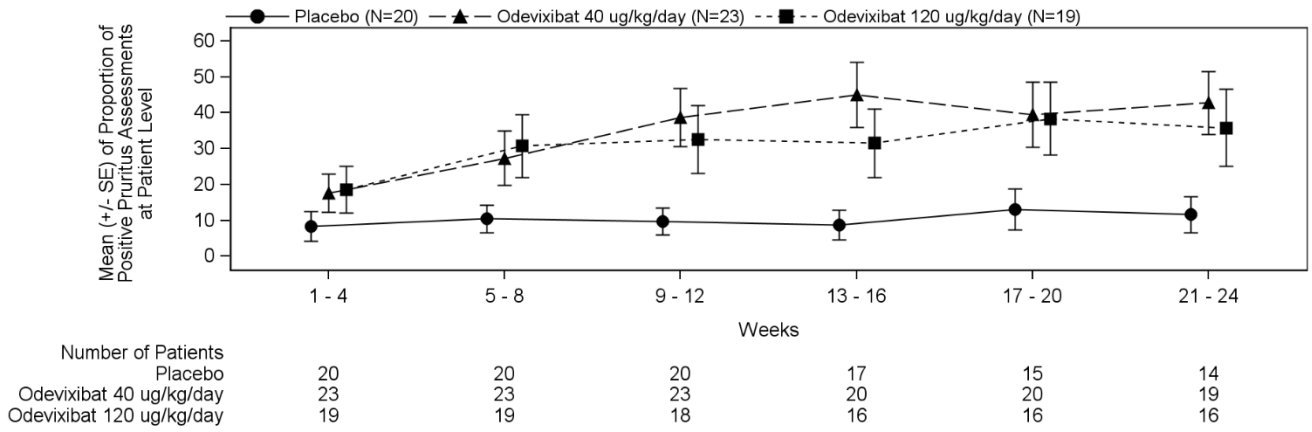
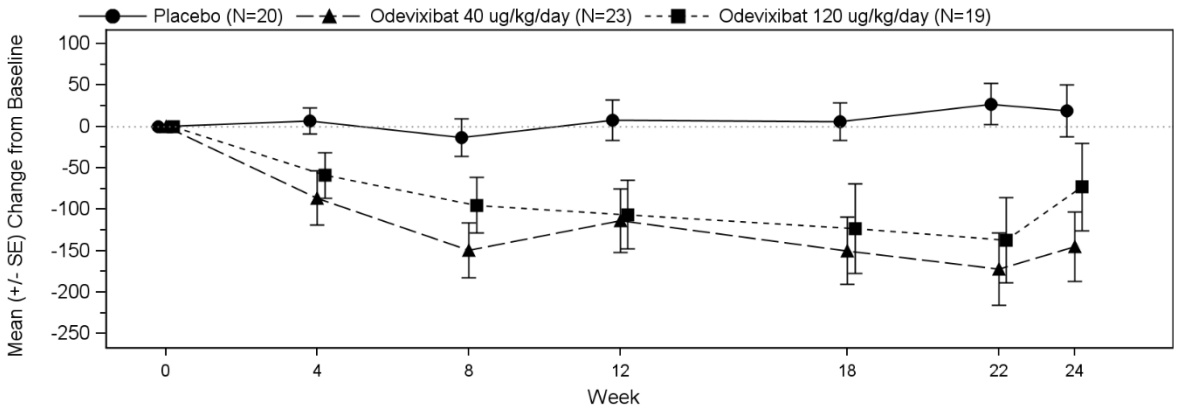


Figure 2: Mean (±SE) change from baseline in serum bile acid concentration (µmol/L) over time



Number of Patients							
Placebo	20	20	18	17	16	12	11
Odevixibat 40 ug/kg/day	23	21	21	20	15	14	17
Odevixibat 120 ug/kg/day	19	19	16	16	11	11	15

Patients completing PFIC Trial 1 were eligible to enrol in PFIC Trial 2 (Study A4250-008), an open-label extension trial in which all patients received odevixibat 120 µg/kg/d for additional 72 weeks. On average, the improvements observed in pruritus and serum bile acids in patients treated with odevixibat in trial PFIC 1 were maintained for 72 weeks.

ALGS

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

The primary endpoint in ALGS Trial 1 was change in pruritus score from baseline to month 6 (Weeks 21 to 24). Pruritus was assessed by an observer once in the morning and once in the evening ("observer reported outcome", ObsRO). With ObsRO the severity of scratching was assessed using a 5-point scale (0-4), from 0 (no scratching) to 4 (the most severe scratching).
Change in serum bile acid levels from baseline to the average of weeks 20 and 24 was the key secondary endpoint.

Median age (range) of the patients in ALGS Trial 1 was 5.45 (0.5 to 15.5) years; 51.9% were male and 82.7% were white. 92.3% of patients had the JAG1 mutation and 7.7% had the NOTCH2 mutation. At baseline, 98.1% of patients were treated with concomitant anti-pruritic medications, including UDCA (88.5%). Overall, 51 (98.1%) of the 52 patients had moderate hepatic impairment and

1 (1.9%) (placebo group) had severe hepatic impairment based on the Child-Pugh classification. Baseline mean (SD) eGFR was 158.65 (51.437) mL/min/1.73 m^2. Baseline mean (SD) ALT, AST, and total bilirubin were 173.7 (84.48) U/L, 167.0 (83.22) U/L, and 55.14 (47.911) µmol/L, respectively. Baseline mean (SD) scratching score (range: 04) and serum bile acids levels were similar in odevixibat treated patients (2.80 [0.520] and 237.4 [114.88] µmol/L, respectively) and placebo treated patients (3.01 [0.636] and 246.1 [120.53] µmol/L, respectively).

Table 5 presents the results of the change from baseline in average pruritus 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 5: Comparison of key efficacy results for odevixibat vs. placebo over the 24-week treatment period (ALGS Trial 1)

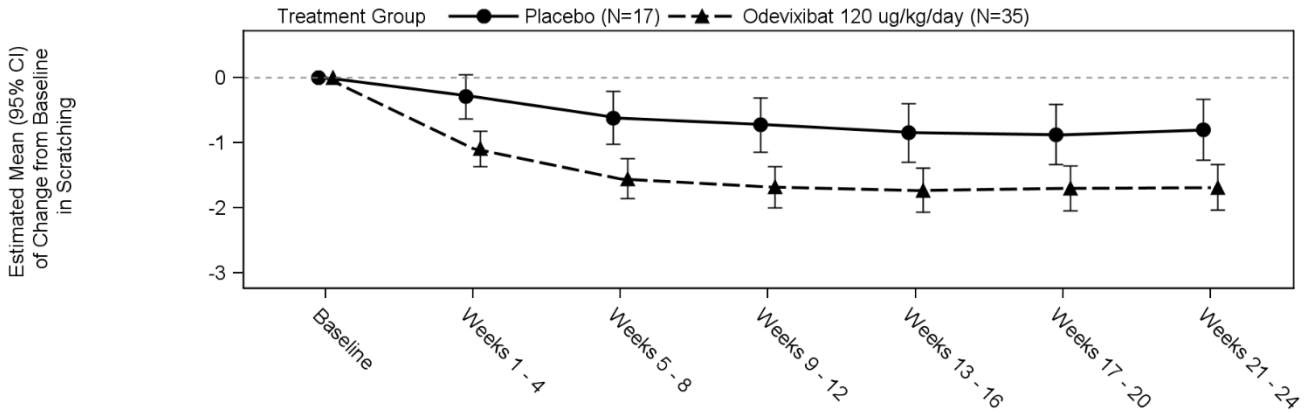
	Placebo (N=17)	**Odevixibat 120 mcg/kg/day (N=35)**
Change from baseline in average pruritus score to Month 6 (Weeks 21 to 24) of treatment		
LS Mean (SE)[a]	-0.80 (0.233)	-1.69 (0.174)
LS Mean difference vs. placebo (95% CI)[a]		-0.88 (-1.44, -0.33)
One-sided p-value[a]		0.0012
Change from baseline in serum bile acid concentration (µmol/L) to the average of Weeks 20 and 24 of treatment		
LS Mean (SE)[a]	22.39 (28.463)	-90.35 (21.336)
LS Mean difference vs. placebo (95% CI)[a]		-112.74 (-178.78, -46.69)
One-sided p-value[a]		0.0006

LS Mean = Least Squares Means

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

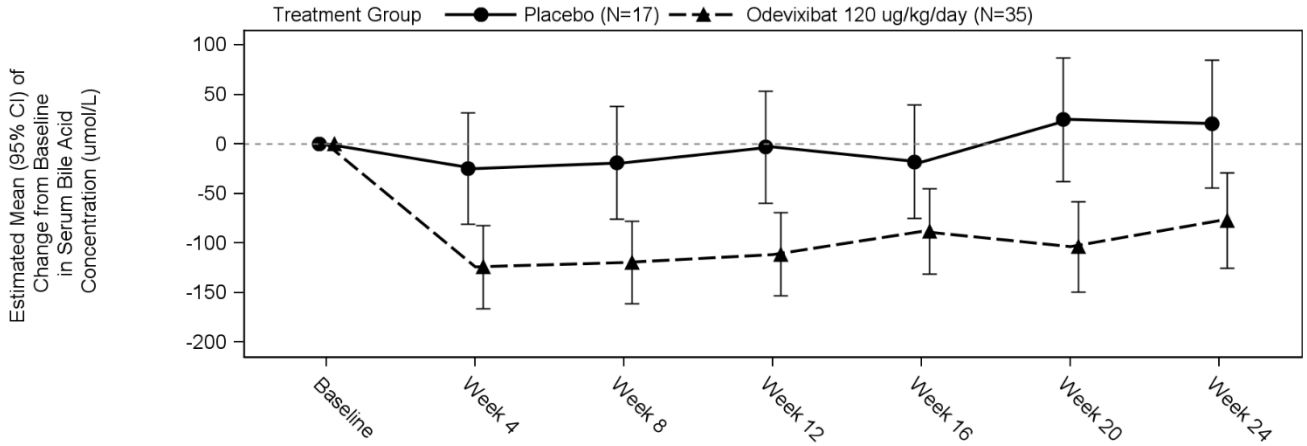
Figures 3 and 4 display graphically the mean (SE) changes from baseline in patients' average pruritus scores and patients' serum bile acid levels, respectively, in each treatment group for each month.in each treatment group for each month.

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



Number of Patients							
Placebo	17	17	17	16	15	17	16
Odevixibat 120 ug/kg/day	35	34	34	34	34	35	34

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



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

Patients who completed ALGS Trial 1 were eligible to enrol in ALGS Trial 2 (Study A4250-015), a 72week open-label extension trial. On average, the improvements observed in pruritus and serum bile acids in ALGS trial 1 in patients treated with odevixibat were maintained for 72 weeks.

Pharmacokinetic properties

Absorption

Odevixibat is minimally absorbed following oral administration; absolute bioavailability data in humans are not available, and estimated relative bioavailability is < 1.5%. Peak odevixibat plasma concentration

(C_{max}) is reached within 1 to 5 hours. Observed exposures in paediatric patients (age between 1.1 and 16.0 years; body weight from 5.6 to 55.2 kg) are limited to trough values; for the 120 mcg/kg/day dose the trough values were below the limit of detection for 88% of the samples in patients with mild hepatic impairment (Child-Pugh A) and for 43% of the samples in patients with moderate hepatic impairment (Child-Pugh B). The maximum observed trough concentrations in Child-Pugh A and B were 0.455 and 3.38 ng/mL, respectively. Simulated C_{max} values in a paediatric PFIC patient population for the 40 and 120 mcg/kg/day doses are 0.211 ng/mL and 0.623 ng/mL, respectively, and AUC values were 2.26 ng × h/mL and 5.99 ng × h/mL, respectively.

Simulated C_{max} and AUC values for the 120 mcg/kg/day dose in a paediatric ALGS population were similar to PFIC. There is minimal accumulation of odevixibat following once-daily dosing.

Effects 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 PFIC patients for the 40 and 120 mcg/kg/day dose regimens are 40.3 and 43.7 L/kg, respectively. The V/F in a typical 70 kg subject is predicted to be 3338 L.

The mean volume of distribution (V/F) in ALGS patients is predicted to be 1160 L. The geometric mean body weight adjusted V/F for ALGS is 57.9 L/kg.

Metabolism

Odevixibat is minimally metabolised in humans.

Elimination

Following administration of a single oral dose of 3 000 mcg of radiolabeled odevixibat in healthy adults, the average percent recovery of the administered dose was 82.9% in faeces; less than 0.002% was recovered in the urine. More than 97% of faecal radioactivity was determined to be unchanged odevixibat.

The mean body weight normalised apparent total clearances (CL/F) in paediatric PFIC patients for the 40 and 120 mcg/kg/day dose regimens are 26.4 and 23.0 L/kg/h, respectively. The CL/F in a typical 70 kg subject is predicted to be 2970 L/h, and the mean half-life is approximately 2.5 hours.
The mean apparent clearance (CL/F) in ALGS patients is predicted to be 212 L/h, and the mean half-life is approximately 4.75 hours. The geometric mean body weight adjusted CL/F for ALGS is 10.5 L/h/kg.

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

Pharmacokinetic/pharmacodynamic relationship(s)
Consistent with the mechanism and site of action of odevixibat in the gastrointestinal tract no relationship between systemic exposure and clinical effects is observed. 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 and all patients with ALGS presented with some degree of hepatic impairment because of the disease. Hepatic metabolism of odevixibat is not a major component of the elimination of odevixibat. No data are available for patients with severe hepatic impairment (Child-Pugh C).
Renal impairment

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

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

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.
Reproductive and developmental toxicity

In pregnant New Zealand White rabbits, early delivery/abortion was observed in two rabbits receiving odevixibat during the period of foetal organogenesis at an exposure multiple of ≥ 2.3 of the anticipated clinical exposure (based on total plasma odevixibat AUC0-24). Reductions in maternal body weight and food consumption were noted in all dose groups (transient at the exposure multiple 1.1 of the anticipated dose).

Starting from the exposure multiple of 1.1 of the clinical human exposure (based on total plasma odevixibat AUC0-24), 7 foetuses (1.3% of all foetuses from odevixibat exposed does) in all dose groups were found to have cardiovascular defects (i.e. ventricular diverticulum, small ventricle and dilated aortic arch).[17] No such malformations were observed when odevixibat was administered to pregnant rats. Because of the findings in rabbits, an effect of odevixibat on cardiovascular development cannot be excluded.

Odevixibat had no effect on the reproductive performance, fertility, embryo-foetal development, or prenatal/postnatal development studies in rats at the exposure multiple of 133 of the anticipated clinical exposure (based on total plasma odevixibat AUC0-24), including juveniles (exposure multiple of 63 of the anticipated human exposure).

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

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

Other information

Shelf life

Do not use this medicine after the expiry date marked as «EXP» on the pack.

Special precautions for storage

Store at 15-30 °C.
Store in the original package in order to protect from light.
Keep out of reach of children.

Marketing authorization number

69600 (Swissmedic)

Packages

High-density polyethylene (HDPE) bottle with a tamper evident, child resistant closure.
200 mcg hard capsules 30 (B)
400 mcg hard capsules 30 (B)
600 mcg hard capsules 30 (B)

1200 mcg hard capsules 30 (B)

Marketing authorization holder

Ipsen Pharma Schweiz GmbH, Zug

Status of information

July 2025