Summary of the Risk Management Plan (RMP)

Name of the medicinal product:	Bylvay
Active substance:	Odevixibat
Version number of the current RMP:	7.0
Name of the marketing authorisation holder:	Ipsen Pharma Schweiz GmbH
Date of RMP:	10 April 2025

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Bylvay is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittel information / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Bylvay in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Ipsen Pharma Schweiz GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Bylvay.

Summary of the Risk Management Plan for Bylvay® (odevixibat)

This is a summary of the risk management plan (RMP) for odevixibat. The RMP details important risks of odevixibat, how these risks can be minimised and how more information will be obtained about odevixibat's risks and uncertainties (missing information).

Odevixibat's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how odevixibat should be used.

This summary of the RMP for odevixibat should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of odevixibat's RMP.

I. The Medicine and What is it Used for

Odevixibat is authorised for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older and cholestatic pruritus in Alagille syndrome (ALGS) in patients aged six months or older (see SmPC for the full indication). Odevixibat is the active substance and it is given orally.

Further information about the evaluation of odevixibat's benefits can be found in odevixibat's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <*https://www.ema.europa.eu/en/medicines/human/EPAR/bylvay*> and <*https://www.ema.europa.eu/en/medicines/human/EPAR/kayfanda*>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of odevixibat, together with measures to minimise such risks and the proposed studies for learning more about odevixibat's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of odevixibat is not yet available, it is listed under 'missing information' below.

II. A List of Important Risks and Missing Information

Important risks of odevixibat are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of odevixibat. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information

Important identified risks	• Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance
Important potential risks	• Hepatotoxicity • Embryo-foetal toxicity • Interactions with fat-soluble drugs
Missing information	• Long-term use • Use during pregnancy and use in breastfeeding women

II. B Summary of Important Risks

Important identified risk, Important potential risk and Missing information

Important identified risk: Clinically significant or severe diarrhoea leading to dehydration and electrolyte imbalance	
Evidence for linking the risk to the medicine	Diarrhoea related to odevixibat treatment was observed in patients with PFIC and in patients with ALGS in the clinical studies. Adverse events of diarrhoea assessed as related to odevixibat were mild to moderate in severity and self-limiting. Diarrhoea is the most commonly reported adverse reaction for investigational drugs of the same class, e.g. volixibat, maralixibat and elobixibat. Study discontinuations in studies of the same drug class were reported due to TEAEs of diarrhoea. In the PFIC pivotal study A4250-005, one patient in the 120 µg/kg/day group in Study A4250-005 discontinued treatment due to an event of clinically significant diarrhoea and experienced an SAE of acute dehydration (severe) requiring hospitalisation. In the long-term extension study A4250-008, as of the 15 February 2024 data cutoff, two patients had discontinued treatment due to diarrhoea. No patient in the ALGS phase III studies discontinued treatment due to diarrhoea. Drug-related diarrhoea was observed in non-clinical studies with mice, rats and dogs. Diarrhoea is the most likely dose-limiting effects of odevixibat as indicated by preliminary toxicity studies.
Risk factors and risk groups	Malabsorption and diarrhoea are known co-morbidities in patients with PFIC and patients with ALGS. Patients with

	PFIC1 are known to show extrahepatic manifestations in the form of persistent diarrhoea. In general, other risk factors for diarrhoea include the following: Malabsorption Biliary diversion surgery (partial external or internal) Paediatric population, more susceptible to viral infections and infections Side effects following liver transplantation Diet and food sensitivities Other medications known to cause diarrhoea
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Minimal signs of reversible, non-adverse liver toxicity were noted in rats (adult and juvenile). The safety margin based on the NOAEL in the juvenile toxicity study is high (based on adult human PK data), about 300-fold, related to both dose and exposure. In the oral carcinogenicity study in mice and rats, gallbladder and biliary hyperplasia / basophilic foci of alteration were of late onset, not adverse and without neoplastic risk. Although slight hepatic effects were noted following odevixibat exposure, they were considered non-adverse in the context of repeated administrations. In the PFIC clinical studies, improvements in liver function tests were noted in odevixibat-treated versus placebo-treated patients. In these clinical studies, most excursions in ALT, AST and total bilirubin were considered related to the underlying disease and/or intermittent concomitant viral illnesses, which are common to paediatric patients. Overall, 52% of patients in the Pooled Phase 3 group had TEAEs in the SMQ of Drug-related Hepatic Disorders – comprehensive search (narrow and broad). The most common TEAEs reported in this SMQ were blood bilirubin increased, INR increased, ALT increased, AST increased, hepatomegaly and jaundice. The majority of TEAEs were mild to moderate in intensity. Eight patients (0.66%) reported severe events from this SMQ, three of which serious and considered by the investigator to be unrelated to study drug. In PFIC clinical trials, Drug Safety Monitoring

	Board (DSMB) was conducting an independent, adjudication of hepatic events. Overall, 69 (57%) of the 121 patients in the Pooled Phase 3 groups had an event that underwent adjudication by the DSMB. Based on review of 69 cases by the DSMB, all but one case (increased ALT and total bilirubin) were adjudicated as unrelated to study treatment.
	In the ALGS phase III clinical trials, no liver decompensation events were reported, nor were there any reports of new or worsening portal hypertension, hepatic cirrhosis, ascites, hepatic encephalopathy or variceal haemorrhage. In Study A4250-012, the overall incidence of liver-related events in the SMQs of *Drug-related hepatic disorders – comprehensive search (narrow and broad), Biliary tract disorders, Gallbladder-related disorders and Gallstone-related disorders*, was similar in the odevixibat and placebo groups (11.0% and 12.0%, respectively). A detailed review of changes from baseline to Week 24 for transaminase levels of the pooled data from studies A4250-012 and A4250-015, showed larger mean increases for ALT and AST for patients who received odevixibat compared with patients who received placebo; for total bilirubin, the changes from baseline were similar in the odevixibat and placebo groups. The increases in ALT and AST were observed by Week 4 and then plateaued through Week 24. Further review of the data based on modified evaluation of drug-induced serious hepatotoxicity (eDISH) plots indicated that none of the patients in either treatment group had ALT elevations >3 × baseline concurrent with total bilirubin >2 × baseline. Three patients, including two in the odevixibat group and one in the placebo group had ALT and AST elevations >3 × baseline without concurrent elevations in total bilirubin >2 × baseline. Review of the pertinent clinical and diagnostic information for the two patients treated with odevixibat suggests that the occurrence of DILI was unlikely.
	No patients in either the PFIC or ALGS clinical trials experienced an event of liver decompensation defined as:
	• INR elevation >1.5 that is refractory to vitamin K administration
	• In a patient who developed portal hypertension and cirrhosis post-baseline, transition to decompensated cirrhosis evidenced by any of the following:
	  • Presence of ascites
	  • Hepatorenal syndrome
	  • Portopulmonary hypertension
	  • Hepatopulmonary syndrome
	  • Variceal haemorrhage
	  • Hepatic encephalopathy
	Generally, odevixibat poses a low hepatotoxicity risk. This important potential risk is based on the odevixibat clinical and non-clinical studies.

Risk factors and risk groups	Patients with cholestatic liver diseases suffer from excess bile acids in the liver, which are thought to play a contributory role in hepatic oxidative stress, inflammation resulting in tissue

	damage, fibrosis, cirrhosis and eventually end-stage liver disease. Other risk factors for hepatotoxicity include the following: Malnourishment Use of potentially hepatotoxic drugs Other underlying co-morbidities (e.g. viral infections or pre-existing liver disease)
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	In an embryo-foetal development study in the rabbit, cardiovascular malformations in foetal rabbits were observed at low frequency (1.3%) at all dosages (10, 30, or 100 mg/kg/day) tested. No findings were observed in the corresponding rat study. Because of the findings in rabbits, an effect of odevixibat on cardiovascular development cannot be excluded.
Risk factors and risk groups	Women of childbearing potential who take odevixibat.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.6 and 5.3 PL section 2 Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Interaction with fat-soluble drugs	
Evidence for linking the risk to the medicine	This risk is related to the background disease pathology and not to odevixibat per se. Fat-soluble vitamin malabsorption has been reported in the patient population [3]. Clinical data to date in patients with PFIC treated with odevixibat for 72 weeks or longer and in patients with ALGS treated for 72 weeks or longer

	has not demonstrated any unwarranted effect on fat-soluble vitamin levels (Vitamin A, D, E) and INR.
Risk factors and risk groups	Fat malabsorption and fat-soluble vitamin deficiencies are known co-morbidities in patients with PFIC and in patients with ALGS. No clinical drug-drug interactions studies have been conducted with other lipophilic drugs. It cannot be excluded that the absorption of lipophilic drugs other than oral contraceptives is affected by odevixibat.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.5 and 4.8 PL section 2 and 4 Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Long-term use	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Legal status: Prescription only medicine. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study A4250-019 Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Use during pregnancy and use in breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Legal status: Prescription only medicine Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Prospective Registry-Based Study of the Long-Term Safety of Odevixibat in Patients with Alagille

	syndrome (ALGS) See section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: ALGS=Alagille syndrome; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CD=controlled document; CSR=clinical study report; EMA=European Medicines Agency; GGT=gamma-glutamyl transferase; INR=international normalized ratio; NOAEL=no observed adverse effect level; PFIC=progressive familial intrahepatic cholestasis; PK=pharmacokinetics; PL=package leaflet; RMP=risk management plan; SAE=serious adverse event; SmPC=Summary of Product Characteristics; SMQ=Standardised MedDRA Query; SOP=standard operating procedure; TEAE=Treatment-Emergent Adverse Event

II. C Post-authorisation Development Plan

II.C. 1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

PFIC

A4250-018 Registry-based Efficacy Study:

Study short name and title:

Prospective Registry-based Study of the Long-term Efficacy of Odevixibat in Patients with PFIC

Purpose of the Study:

To assess the time to biliary diversion surgery, liver transplantation and death for the overall population of patients with PFIC as well as the populations of patients with different PFIC subtypes and to compare the outcomes in odevixibat-treated and untreated patients.

ALGS

Registry-based Safety Study:

Study short name and title:

Prospective Registry-based Study evaluating the Long-term Safety of Odevixibat in Patients with Alagille syndrome (ALGS)

Purpose of the study:

The aim of this study is to assess the long-term, real-world safety profile of odevixibat treatment in patients with ALGS using prospectively collected data.

II.C.2 Other studies in post-authorisation development plan

A4250-019 Registry-based Safety study

Study short name and title:

Prospective Registry-based Study of the Long-term Safety of Odevixibat in Patients with PFIC

Purpose of the Study:

- Assess the long-term, real-world safety profile of odevixibat treatment in patients with PFIC compared to patients not receiving odevixibat (untreated control cohort).