

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Lyvdelzi 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains seladelpar lysine dihydrate equivalent to 10 mg seladelpar.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Size 1 (26.1 mm x 9.4 mm) hard capsules with dark blue opaque cap and light grey opaque body imprinted with “CBAY” in white ink on the cap and “10” in black ink on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lyvdelzi is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.

4.2 Posology and method of administration

Posology

The recommended dose of seladelpar is 10 mg once daily.

Missed dose

If a dose of seladelpar is missed, the patient should take the subsequent dose at the next scheduled time point. A double dose should not be taken to make up for the missed dose.

Special populations

Elderly

Limited data exists in elderly patients. No dose adjustment is required for elderly patients (see section 5.2).

Renal impairment

No dose adjustment of seladelpar is required for patients with mild, moderate and severe renal impairment (see section 5.2).

Patients with end-stage renal disease on dialysis have not been studied. No dose recommendation can be provided for this group.

Hepatic impairment

No dose adjustment is required in PBC patients with mild hepatic impairment (Child-Pugh A).

Safety and efficacy of seladelpar have not been established in PBC patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

Consider discontinuing seladelpar if the patient progresses to moderate hepatic impairment. Use is not recommended in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

There is no relevant use of seladelpar in the paediatric population in the treatment of PBC.

Method of administration

Oral use. The capsules can be taken with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Liver test abnormalities

Dose dependent increases in serum transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) have been observed in patients receiving higher doses of seladelpar (see section 4.9). Obtain baseline clinical and laboratory assessments at initiation of treatment with seladelpar and monitor thereafter according to routine clinical practice. Consider temporary interruption of seladelpar treatment if liver tests worsen, or the patient develops signs and symptoms consistent with liver dysfunction. Consider permanent discontinuation if liver tests worsen again after restarting seladelpar.

Biliary Obstruction

Avoid use of seladelpar in patients with complete biliary obstruction. If biliary obstruction is suspected, interrupt seladelpar and treat as clinically indicated.

Co-administration of other medicinal products

Co-administration of probenecid with seladelpar is not recommended (see section 4.5).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on seladelpar

Probenecid

Concomitant administration of seladelpar with probenecid (an OAT1, OAT3 and OATP1B1-inhibitor) is not recommended (see section 4.4).

In a dedicated clinical drug interaction study, seladelpar area under the curve from zero to time infinity ($AUC_{0-\infty}$) increased by 2-fold and maximum serum concentration (C_{max}) by 4.69-fold following concomitant use of a single 10 mg seladelpar dose with 500 mg probenecid in healthy subjects.

Inhibitors of drug transporters

Concomitant administration of seladelpar with dual or multiple clinical inhibitors of drugs transporters including BCRP, OATP1B1, OATP1B3 and OAT3 (e.g cyclosporine) may result in an increase of seladelpar exposure. When seladelpar is concomitantly administered with dual or multiple clinical inhibitors of drugs transporters including BCRP, OATP1B1, OATP1B3, and OAT3, patients should be closely monitored for adverse effects.

In a dedicated clinical drug interaction study, seladelpar $AUC_{0-\infty}$ increased by 2.1-fold and C_{max} by 2.9-fold following concomitant use of a single 10 mg seladelpar dose with 600 mg cyclosporine (a BCRP, OATP1B1, OATP1B3 and CYP3A4 inhibitor) in healthy subjects.

CYP2C9 and CYP3A4 inhibitors

Seladelpar is primarily metabolized *in vitro* by CYP2C9 and to a lesser extent by CYP2C8 and CYP3A4. Concomitant administration of seladelpar with medicines that are strong CYP2C9 inhibitors, or dual moderate CYP2C9 and moderate-to-strong CYP3A4 inhibitors may result in an increase in seladelpar exposure. When seladelpar is concomitantly administered with medicinal products that are strong CYP2C9 inhibitors, or dual moderate CYP2C9 and moderate to strong CYP3A4 inhibitors (e.g. fluconazole, mifepristone), patients should be closely monitored for adverse effects.

In a dedicated clinical drug interaction study, seladelpar $AUC_{0-\infty}$ increased by 2.4-fold and C_{max} by 1.4-fold following concomitant use of a single 10 mg seladelpar dose with 400 mg fluconazole (moderate CYP2C9 and CYP3A4 inhibitor) in healthy subjects.

CYP2C9 inducers and strong CYP3A4 inducers

Concomitant administration of seladelpar with medicines that are CYP2C9 inducers and strong CYP3A4 inducers (e.g. rifampicin, a strong CYP3A4 and moderate CYP2C9 inducer) can decrease seladelpar exposure. When seladelpar is concomitantly administered with medicinal products that are CYP2C9 inducers and strong CYP3A4 inducers, patients should be monitored for a potential reduction in efficacy.

Seladelpar $AUC_{0-\infty}$ decreased by approximately 44% and C_{max} by 24% following administration of a single 10 mg seladelpar dose after carbamazepine 300 mg twice daily in healthy subjects. The carbamazepine (a strong CYP3A and weak CYP2C9 inducer) dose was escalated from 100 mg to 300 mg over 7 days.

Bile acid binding resins

Bile acid binding resins such as cholestyramine, colestipol, or colesevelam, may reduce the absorption of other medicinal products administered concurrently. Patients should take seladelpar at least 4 hours before or 4 hours after taking a bile acid binding resin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of seladelpar in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant exposure levels (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of seladelpar during pregnancy.

Breast-feeding

It is unknown whether seladelpar or its metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from seladelpar therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No human data on the effect of seladelpar on fertility are available.

Animal studies do not indicate any direct or indirect effects on fertility or the ability to reproduce.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

Based on clinical trial experience, the most frequently reported adverse reactions were abdominal pain (11.1%), headache (7.2%), nausea (6.5%) and abdominal distension (3.9%). These adverse reactions were non-serious and did not lead to discontinuation of seladelpar.

Tabulated list of adverse reactions

The frequencies of the adverse drug reactions provided in the table below are based on pooled data from the RESPONSE and ENHANCE trials unless otherwise stated.

Frequencies are defined according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ to $< 1/1\ 000$); very rare ($< 1/10\ 000$); not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions reported in clinical trials in patients treated with seladelpar

System Organ Class	Very Common	Common
Nervous System Disorders		Headache
Gastrointestinal Disorders	Abdominal pain ^a	Nausea Abdominal distension

^a Includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

Reporting of suspected adverse reactions

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

4.9 Overdose

PBC patients who received 5 times the recommended dose or 20 times the recommended dose of seladelpar experienced an increase in liver transaminases, muscle pain, and/or elevations in creatine phosphokinase, which resolved upon seladelpar discontinuation. Dose dependent increases in serum creatinine were also observed.

There is no specific treatment for overdose with seladelpar. General supportive care of the patient is indicated, as appropriate. If indicated, elimination of unabsorbed medicinal product should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because seladelpar is highly bound to plasma proteins, haemodialysis should not be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, other drugs for bile therapy. ATC code: A05AX07

Mechanism of action

Seladelpar is a peroxisome proliferator-activated receptor delta (PPAR δ) agonist, or delpar. PPAR δ is a nuclear receptor expressed in the liver and other tissues. PPAR δ activation reduces bile acid synthesis in the liver through Fibroblast Growth Factor 21 (FGF21) -dependent downregulation of CYP7A1, the key enzyme for the synthesis of bile acids from cholesterol and by decreasing cholesterol synthesis and absorption. These actions result in lower bile acid exposure in the liver and reduced circulating bile acid levels.

Pharmacodynamic effects

In clinical studies, reduction in ALP was observed within 1 week, continued to decrease through Month 3, and was sustained through Month 24.

In RESPONSE, treatment with seladelpar led to a decrease in Interleukin-31 (IL-31) after 6 and 12 months of treatment in patients with moderate to severe pruritus.

Clinical efficacy and safety

The efficacy of seladelpar was evaluated in patients with PBC in a randomised, double-blind, placebo-controlled, 12-month trial (RESPONSE). Patients were included in the trial if their ALP was 1.67-times upper limit of normal (ULN) or greater and total bilirubin was less than or equal to 2-times ULN. Patients were excluded from the trial if they had other chronic liver diseases, clinically important hepatic decompensation including portal hypertension with complications, or cirrhosis with complications (e.g., Model for End Stage Liver Disease [MELD] score of 12 or greater, known oesophageal varices or history of variceal bleeds, history of hepatorenal syndrome). A 14-day run-in period prior to randomisation was used to establish a baseline itch intensity, as measured by the patient-reported daily 24-hour Numerical Rating Scale (Pruritus-NRS) scores (0 “no itch” to 10 “worst itch imaginable”).

Patients were randomised (2:1) to receive either seladelpar (n = 128) 10 mg once daily; or placebo (n = 65) for 12 months. Seladelpar or placebo was administered in combination with UDCA in 181 (94%) patients during the trial, or as a monotherapy in 12 (6%) patients who were unable to tolerate UDCA.

The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. Of the 193 randomised patients, the mean age was 56.7 years (range 28-75 years); 41 (21%) were aged 65 years or older; 183 (95%) were female; 170 (88%) were White, 11 (6%) were

Asian, 4 (2%) were Black or African American, 6 (3%) were American Indian or Alaska Native. A total of 56 (29%) patients identified as Hispanic/Latino.

The mean baseline ALP concentration was 314.3 U/L, corresponding to 2.7-times ULN. The mean baseline total bilirubin concentration was 0.758 mg/dL and was less than or equal to the ULN in 87% of the enrolled patients. At baseline patients in the study population had the following elevations in other liver biochemistries: alanine aminotransferase (ALT) 1.2-times the ULN, aspartate aminotransferase (AST) 1.2-times the ULN, and gamma-glutamyl transferase (GGT) 1.7-times the ULN. The baseline mean (SD) pruritus NRS score was 3.0 (2.85). Among enrolled patients, 49 (38%, mean NRS score 6.1) in the seladelpar 10 mg arm and 23 (35%, mean NRS score 6.6) in the placebo arm had moderate to severe pruritus (NRS score ≥ 4) at baseline (mean baseline NRS score 6.3).

Cirrhosis (Child-Pugh A) was present at baseline in 18 patients (14%) in the seladelpar 10 mg arm, and 9 patients (14%) in the placebo arm.

In RESPONSE, the primary endpoint was a responder analysis at Month 12, where response was defined as a composite of three criteria: ALP less than 1.67-times the ULN, total bilirubin \leq ULN, and an ALP decrease of at least 15%. The ULN for ALP was defined as 116 U/L for females and males. The ULN for total bilirubin was defined as 1.1 mg/dL for females and males. ALP normalisation was defined as achieving ALP less than ≤ 1.0 -times the ULN. The pruritus improvement was assessed by change from baseline in weekly averaged pruritus NRS score at Month 6 in patients with NRS score ≥ 4 at baseline.

The results for the primary composite endpoint and ALP normalisation are presented in Table 2.

Table 2: RESPONSE trial: Composite biochemical endpoint and ALP normalisation with seladelpar with or without UDCA^a

	Seladelpar 10 mg (N = 128)	Placebo (N = 65)	Treatment difference % (95% CI) ^e
Primary composite endpoint at Month 12^b			
Responder rate, (%) ^c [95 % CI]	62 [53, 70]	20 [10, 30]	42 (28, 53)
Components of primary endpoint			
ALP less than 1.67-times ULN, (%)	66	26	39 (25, 52)
Decrease in ALP of at least 15%, (%)	84	32	51 (37, 63)
Total bilirubin less than or equal to ULN ^d , (%)	81	77	4 (-7, 17)
ALP normalisation			
ALP normalisation at Month 12, $\leq 1.0 \times$ ULN (%) ^c [95% CI]	25 [18, 33]	0 [0, 0]	25 (18, 33)

N = Number

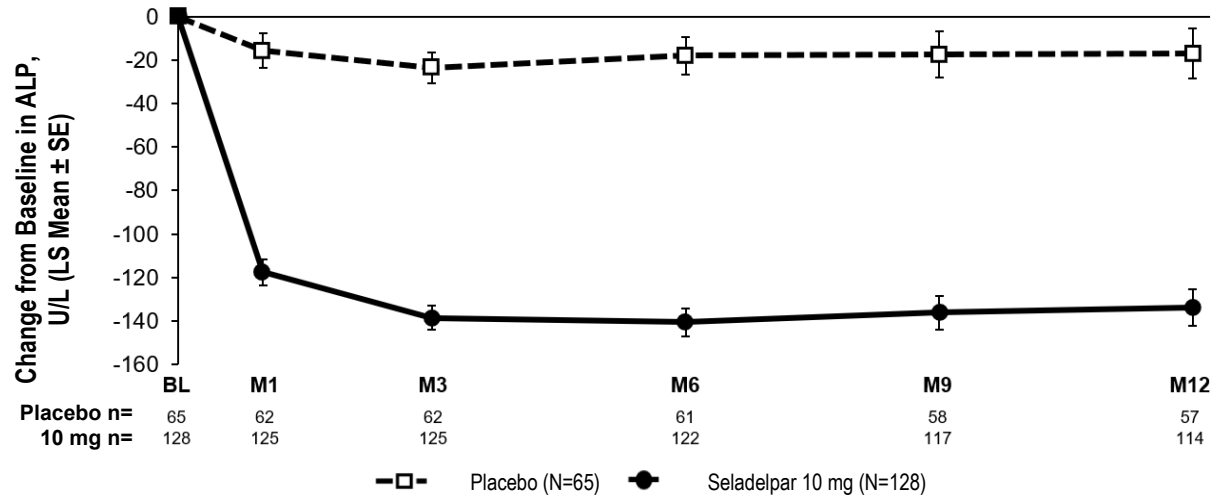
CI = Confidence Interval

- a In the trial there were 12 patients (6%) who were intolerant to UDCA and initiated treatment as monotherapy: 8 subjects (6%) in the seladelpar 10 mg arm, and 4 patients (6 %) in the placebo arm.
- b Percentage of patients achieving a response, defined as an ALP value less than 1.67-times the ULN, an ALP decrease of at least 15%, and total bilirubin less than or equal to the ULN. Patients with missing values were considered as not achieving response.
- c $p < 0.0001$ for seladelpar 10 mg versus placebo. P-value was obtained using the Cochran–Mantel–Haenszel Test stratified by baseline ALP level < 350 U/L versus ALP level ≥ 350 U/L, and baseline pruritus NRS < 4 versus ≥ 4 .
- d The mean baseline total bilirubin value was 0.758 mg/dL and was less than or equal to the ULN in 87% of the enrolled patients.
- e 95% unstratified Miettinen and Nurminen confidence intervals (CIs) are provided.

Alkaline phosphatase (ALP)

Figure 1 shows the mean reductions in ALP in seladelpar-treated patients compared to placebo. Reductions were observed at Month 1, continued through Month 6, and were sustained through Month 12.

Figure 1: Change from baseline in ALP over 12 months in RESPONSE by treatment arm with or without UDCA^a



a In the trial there were 12 patients (6%) who were intolerant to UDCA and initiated treatment as monotherapy: 8 patients (6%) in the seladelpar 10 mg arm and 4 patients (6%) in the placebo arm.

Among the subset of patients with ALP < 350 U/L (< approximately 3-times ULN) at baseline, 76% (71/93) and 23% (11/47) of patients achieved a response at Month 12, in the seladelpar 10 mg and placebo arms, respectively. For patients with ALP ≥ 350 U/L at baseline, 23% (8/35) and 11% (2/18) of patients achieved a response at Month 12, in the seladelpar 10 mg and placebo arms, respectively.

Lipid Parameters

The LS means difference from placebo in percentage change from baseline in total cholesterol, LDL-C, and triglycerides was -4.4 (95% CI: -8.5, -0.3) mg/dL, -9.0 (95% CI: -15.0, -2.9) mg/dL, and -15.1 (95% CI: -22.1, -8.1), respectively at month 12. High density lipoprotein-cholesterol remained stable on treatment with seladelpar.

Pruritus

Seladelpar significantly reduced pruritus compared to placebo at Month 6 in patients with baseline average pruritus scores ≥ 4 as assessed by pruritus NRS score, a key secondary endpoint in the RESPONSE trial (Table 3). Seladelpar led to decreased patient-reported pruritus intensity by Month 1 which continued to decrease to Month 6.

Table 3. Change from Baseline in Pruritus Score at Month 6 in RESPONSE in PBC Patients with Moderate to Severe Pruritus at Baseline^a

	Seladelpar 10 mg (N=49)	Placebo (N=23)	Treatment difference % (95% CI)
Baseline average pruritus score, Mean (SD)^b	6.1 (1.4)	6.6 (1.4)	-
Change from baseline in pruritus score at Month 6^c			
Mean (SE)	-3.2 (0.28)	-1.7 (0.41)	-1.5 (-2.5, -0.5) ^d

^a Assessed using the pruritus NRS, which evaluated patients' daily worst itching intensity on an 11-point rating scale with scores ranging from 0 ("no itching") to 10 ("worst itching imaginable"). The pruritus NRS was administered daily in a ≥ 14 -day run-in period prior to randomization through Month 6. Moderate to severe pruritus was defined as a pruritus NRS score ≥ 4 .

^b Baseline included mean of all daily recorded scores during the run in-period and on Day 1. The pruritus scores for each patient for post-baseline months were calculated by averaging the pruritus NRS scores within the scheduled week each month.

^c Based on LS means from a mixed-effect model for repeated measures (MMRM) for change from baseline at Months 1 (Week 4), 3 (Week 12), and 6 (Week 26) accounting for baseline average pruritus score, baseline ALP level (<350 U/L versus ALP level ≥ 350 U/L), treatment arm, time (in months), and treatment-by-time interaction.

^d $p < 0.005$ for seladelpar 10 mg versus placebo.

The effect of seladelpar on pruritus was also assessed by additional patient-reported outcome measures in RESPONSE. At Month 6, an improvement in pruritus, as observed by reductions in total scores of the PBC-40 Itch Domain and 5-D Itch scale, was seen with seladelpar. (Table 4).

Table 4. Change from baseline in PBC-40 Itch Domain and 5-D Itch Scale total scores at Month 6 in RESPONSE in PBC patients with moderate to severe pruritus at baseline

	Seladelpar 10 mg (N=49)	Placebo (N=23)	Treatment difference % (95% CI)
PBC-40 Itch Domain^a			
Mean (SE)	-2.2 (0.38)	-0.40 (0.60)	-1.8 (-3.2, -0.39)
5-D Itch Scale^b			
Mean (SE)	-4.7 (0.53)	-1.3 (0.80)	-3.4 (-5.3, -1.5)

^a LS means were obtained using MMRM for change from baseline at Month 6 accounting for baseline PBC-40 Quality of Life Itch Domain score, baseline ALP level (<350 U/L versus ALP level ≥ 350 U/L), treatment arm, time (in months), and treatment-by-time interaction.

^b LS means were obtained using MMRM for change from baseline at Month 6 accounting for baseline 5-D Itch scale, baseline ALP level (<350 U/L versus ALP level ≥ 350 U/L), time (in months), treatment arm, and treatment-by-time interaction.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with seladelpar in all subsets of the paediatric population in treatment of primary biliary cholangitis (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme.

This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review any new information on this medicinal product at least every year and this SmPC will be updated as necessary

5.2 Pharmacokinetic properties

Absorption

Following oral administration of a single dose of seladelpar 10 mg, seladelpar was readily absorbed with median time to peak concentration (t_{max}) of approximately 1.5 hours.

Seladelpar exposure increased approximately dose-proportionally with single doses from 2 mg to 15 mg, after which the increase in C_{max} was larger than dose-proportional.

Seladelpar showed no evidence of meaningful drug accumulation after multiple daily dosing, and steady-state was achieved from day 4 onwards after daily dosing.

Co-administration of seladelpar with food delayed the t_{max} by 2.5 hours relative to fasted conditions and resulted in an approximately 32% reduction in the C_{max} of seladelpar. As the overall exposure (AUC) is similar, the effects of food on seladelpar pharmacokinetics are not considered clinically relevant.

Distribution

In PBC patients, the steady state apparent volume of distribution of seladelpar is approximately 110.3 L. Plasma protein binding of seladelpar is greater than 99%.

Biotransformation

Seladelpar is primarily metabolized by CYP2C9 and to a lesser extent by CYP2C8 and CYP3A4. M2 is a major metabolite observed in human plasma, accounting for 17.6% of the total plasma radioactivity in the mass balance study and approximately doubling the plasma exposure compared to seladelpar. M2 is not expected to have clinically relevant pharmacological effects.

Elimination

In PBC patients, the apparent oral clearance of seladelpar is 12.6 L/h. Following administration of a single dose of 10 mg seladelpar in healthy subjects, mean elimination half-life was 6 hours for seladelpar. In PBC patients, the half-life range was 3.8 to 6.7 hours for seladelpar.

Following administration of an oral dose of radiolabelled seladelpar, 92.9% of radioactivity was recovered: 73.4% in urine and 19.5% in faeces. Urinary excretion of the dose as unchanged seladelpar was negligible (less than 0.01%).

Characteristics in specific groups or special populations

CYP2C9 genotype

Seladelpar is primarily metabolised *in vitro* by CYP2C9 which is a polymorphic enzyme. Seladelpar plasma exposure (dose-normalised AUC_{0-inf}) was 18% higher in CYP2C9 intermediate metabolisers (*1/*2, *1/*8, *1/*3, *2/*2, n=28) compared to CYP2C9 normal metabolisers (*1/*1, n=84) after a single dose of seladelpar 1 mg to 15 mg. No conclusion could be made for poor metabolisers due to only one identified subject with *2/*3 and no subjects with *3/*3 were identified.

Age, weight, gender and race

Based on population pharmacokinetic analysis, age (19 to 79 years old), weight (45.8 to 127.5 kg), gender, and race (White, Black, Asian, other) do not have a clinically meaningful effect on the pharmacokinetics of seladelpar. No dose adjustments are warranted based on these factors.

Renal impairment

In a dedicated clinical study of patients with mild ($eGFR \geq 60$ to < 90 mL/min), moderate ($eGFR \geq 30$ to < 60 mL/min), and severe (< 30 mL/min and not on dialysis) renal impairment, the AUC_{0-inf} of

seladelpar was 48%, 33% and 3% greater than in patients with normal renal function, respectively, after administration of a single 10 mg dose of seladelpar. The C_{max} of seladelpar was similar in patients with renal impairment, compared to patients with normal renal function. These differences in seladelpar AUC_{0-inf} are not considered to be clinically meaningful. No dose adjustment of seladelpar is required for patients with mild, moderate, or severe renal impairment.

The pharmacokinetics of seladelpar have not been studied in patients requiring haemodialysis.

Hepatic impairment

Based on a clinical pharmacology study in subjects with mild, moderate, and severe hepatic impairment (Child-Pugh A, B, and C, respectively), seladelpar AUC was increased 1.10, 2.52, and 2.12-fold, and C_{max} was increased 1.33, 5.19, and 5.03-fold, respectively, compared to subjects with normal hepatic function.

In an additional study, seladelpar exposures (C_{max} , AUC) were 1.7 to 1.8-fold higher in PBC patients with mild hepatic impairment (Child-Pugh A) with portal hypertension, 1.6 to 1.9-fold higher in PBC patients with moderate hepatic impairment (Child-Pugh B), and 2.1 to 2.5-fold higher in PBC patients with severe hepatic impairment (Child-Pugh C), compared to PBC patients with mild hepatic impairment without portal hypertension, after a single oral dose of 10 mg seladelpar.

Following administration of 10 mg seladelpar once daily for 28 days in PBC patients with mild hepatic impairment (Child-Pugh A) with portal hypertension and PBC patients with moderate hepatic impairment (Child-Pugh B), there was no clinically meaningful accumulation of seladelpar (accumulation ratios were less than 1.2-fold).

Drug interaction studies

Effect of seladelpar on other medicinal products

Seladelpar has no clinically relevant effect on the pharmacokinetics of tolbutamide (CYP2C9 substrate), midazolam (CYP3A4 substrate), simvastatin (CYP3A4 and OATP substrate), atorvastatin (CYP3A4 and OATP substrate), and rosuvastatin (BCRP and OATP substrate).

Effect of other medicinal products on seladelpar

P-gp inhibitor

In a dedicated clinical drug interaction study, seladelpar exposures were not significantly altered when a single dose of 600 mg quinidine (a P-gp inhibitor) was co-administered in healthy subjects.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction and development.

Reproductive and developmental toxicity

Seladelpar did not cause any foetal malformations or effects on embryo-foetal survival or growth in rats or rabbits. In rats, the exposure at NOAEL was 145-fold higher than the clinical AUC at the recommended dose of 10 mg, and 2-fold the clinical AUC in rabbits.

Oral administration of seladelpar at doses of 0, 5, 20 or 100 mg/kg/day in rats during gestation and lactation resulted in a dose-dependent reduction in pup body weights during the pre-weaning period at all dose levels, which was associated with slightly reduced pre-weaning survival at 100 mg/kg/day. Growth-related delays in developmental milestones were noted (eye opening and pinna unfolding at ≥ 5 mg/kg/day; hair growth and sexual maturity at 100 mg/kg/day). Growth reductions at 100 mg/kg/day continued into the post-weaning maturation period and were considered adverse. The exposure at the NOAEL of 20 mg/kg/day was 15-fold the clinical AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Microcrystalline cellulose
Mannitol
Croscarmellose sodium
Butyl hydroxytoluene
Magnesium stearate
Colloidal silicon dioxide

Capsule shell

Gelatin
Titanium dioxide
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)
Indigo carmine (E132)

Black ink used to imprint “10” (on the body of the capsule shell contains)

Shellac (E904)
Propylene glycol (E1520)
Potassium hydroxide (E525)
Black iron oxide (E172)

White ink used to imprint “CBAY” (on the cap of the capsule contains)

Shellac (E904)
Propylene glycol (E1520)
Sodium hydroxide (E524)
Povidone (E1201)
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Lyvdelzi hard capsules are packaged in a high density polyethylene bottle closed with a polypropylene child resistant cap containing an induction seal. Each bottle contains 30 capsules.

The following pack sizes are available: outer cartons containing 1 bottle of 30 hard capsules and outer cartons containing 90 (3 bottles of 30) hard capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER

EU/1/24/1898/001
EU/1/24/1898/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 February 2025
Date of latest renewal: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Gilead Sciences Ireland UC
IDA Business and Technology Park
Carrigtohill
Co. Cork
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of seladelpar in the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA, the MAH shall conduct and submit the final results of the phase III randomised, placebo-controlled clinical study (AFFIRM) to evaluate the efficacy and safety of seladelpar on	February 2031

Description	Due date
long-term clinical outcomes in adults with Primary Biliary Cholangitis (PBC) and compensated cirrhosis according to an agreed protocol.	

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lyvdelzi 10 mg hard capsules
seladelpar

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule contains seladelpar lysine dihydrate equivalent to 10 mg seladelpar.

3. LIST OF EXCIPIENTS

See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules
90 (3 bottles of 30) hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1898/001 30 hard capsules.
EU/1/24/1898/002 90 (3 bottles of 30) hard capsules.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lyvdelzi 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Lyvdelzi 10 mg hard capsules
seladelpar

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule contains seladelpar lysine dihydrate equivalent to 10 mg seladelpar.

3. LIST OF EXCIPIENTS

See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.

Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1898/001 30 hard capsules.
EU/1/24/1898/002 90 (3 bottles of 30) hard capsules.

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lyvdelzi 10 mg hard capsules seladelpar

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

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

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

What is in this leaflet

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

1. What Lyvdelzi is and what it is used for

What Lyvdelzi is

Lyvdelzi contains the active substance seladelpar. It belongs to a group of medicines called peroxisome proliferator-activated receptor delta agonists.

This medicine is used in adults to treat primary biliary cholangitis (PBC), a type of liver disease in which the bile ducts are slowly destroyed, making it harder for bile to flow through. Bile is a fluid that helps digest food, especially fats. When the bile cannot flow into the digestive tract, it backs up in the liver (this is called cholestasis), where it damages liver tissues. This can decrease liver function and cause inflammation. Lyvdelzi can be used together with ursodeoxycholic acid (UDCA), or by itself in patients who cannot use UDCA.

The active substance in Lyvdelzi, seladelpar, works by activating the PPAR delta receptor. This protein regulates levels of bile acids, inflammation, and fibrosis (formation of scar tissue). This reduces the production and the build-up of bile in the liver and also reduces inflammation of the liver.

2. What you need to know before you take Lyvdelzi

Do not take Lyvdelzi:

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

Warnings and precautions

Your doctor may do blood tests before you start Lyvdelzi and during treatment to check how well your liver is working (liver function). Your doctor may need to pause your treatment if these tests show that your liver function worsens. They may then start it again if your liver recovers. If your liver function worsens again after restarting treatment your doctor may permanently stop treatment with Lyvdelzi.

Contact your doctor immediately if you develop symptoms of liver dysfunction (inflammation of the liver) or complete biliary obstruction (blocked bile duct) during treatment including:

- belly (abdominal) pain
- jaundice (yellowing of the skin and the whites of the eyes)
- dark urine
- light coloured stools

Children and adolescents

Lyvdelzi must not be given to children and adolescents below 18 years of age.

Other medicines and Lyvdelzi

Tell your doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines or herbal remedies.

In particular, tell your doctor, pharmacist or nurse if you are taking medicines called:

- Probenecid, used to treat gout
- Cyclosporine, used to prevent the body from rejecting a transplanted organ
- ‘bile acid binding resins’ (such as cholestyramine, colestipol, or colestevlam adsorb) - used to lower blood cholesterol levels. These may make Lyvdelzi work less well if taken too close to when you take Lyvdelzi.
- If you are taking a ‘bile acid binding resin’, you will need to take Lyvdelzi at least 4 hours before or at least 4 hours after taking a ‘bile acid binding resin’. See section 3 for more information.

The following medicines may increase the risk of side effects with Lyvdelzi by increasing the amount of Lyvdelzi in the blood:

- Fluconazole, used to treat fungal infections
- Mifepristone, used for the medical termination of a pregnancy

Pregnancy and breastfeeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using tools or machines

This medicine is not likely to affect you being able to drive, cycle or use any tools or machines.

Lyvdelzi contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially ‘sodium-free’.

3. How to take Lyvdelzi

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with your doctor pharmacist or nurse if you are not sure.

How much to take

The recommended dose is one 10 mg capsule taken once daily.

How to take

- Swallow the capsule whole, with water
- You can take this medicine with or without food
- Lyvdelzi is taken either together with another medicine called ‘ursodeoxycholic acid’ (UDCA, also called urso or ursodiol) – or by itself if you cannot take UDCA.

If you are already taking a bile acid binding resin:

- Take Lyvdelzi at least 4 hours before -or at least 4 hours after-taking the bile acid binding resin

- If you are unsure, ask your doctor, pharmacist or nurse

If you take more Lyvdelzi than you should

If you take more Lyvdelzi than you should, tell your doctor, pharmacist or nurse straight away.

Symptoms of overdose may include dark urine or muscle pain.

If you forget to take Lyvdelzi

If you forget to take Lyvdelzi, skip the missed dose and take the next dose when it is due.

Do not take a double dose to make up for the one that you missed.

If you stop taking Lyvdelzi

Do not stop taking this medicine without talking to your doctor, pharmacist or nurse.

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

4. Possible side effects

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

Side effects

Tell your doctor, pharmacist or nurse if you notice any of the following side effects.

Very common: may affect more than 1 in 10 people

- belly (abdominal) pain

Common: may affect up to 1 in 10 people

- headache
- feeling sick (nausea)
- swelling of the belly (abdominal distension)

Reporting of side effects

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

5. How to store Lyvdelzi

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

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

Do not store this medicine above 30°C.

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

6. Contents of the pack and other information

What Lyvdelzi contains

- The active substance is seladelpar.
- Each hard capsule of Lyvdelzi contains 10 mg of seladelpar.
- The other ingredients are:
 - capsule content – microcrystalline cellulose, mannitol, croscarmellose sodium, butyl hydroxytoluene, magnesium stearate, colloidal silicon dioxide
 - capsule shell – gelatin, titanium dioxide, black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), indigo carmine (E132)
 - black ink used to imprint “10” on the body of the capsule shell – Shellac (E904), propylene glycol (E1520), potassium hydroxide (E525), black iron oxide (E172)
 - white ink used to imprint “CBAY” on the cap of the capsule – Shellac (E904), propylene glycol (E1520), sodium hydroxide (E524), povidone (E1201), titanium dioxide

Do not take Lyvdelzi if you are allergic to any of the ingredients, as described in section 2.

What Lyvdelzi looks like and contents of the pack

This medicine is a hard capsule with a dark blue opaque cap and a light grey opaque body, printed with “CBAY” in white ink on the cap and “10” in black ink on the body. The capsules are packaged in a bottle with a child resistant cap. Each bottle contains 30 capsules. Single packs contain 1 bottle of 30 capsules, and packs made up of 3 bottles contain a total of 90 capsules (3 bottles each containing 30 capsules).

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

Manufacturer

Gilead Sciences Ireland UC
IDA Business and Technology Park
Carrigtohill
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This leaflet was last revised in .

This medicine has been given ‘conditional approval’.

This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

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